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CORSO DI LAUREA MAGISTRALE IN
PSICOBIOLOGIA E NEUROSCIENZE COGNITIVE

Neuropsicologia e telemedicina:
Uno studio di fattibilità per lo screening del declino cognitivo

Neuropsychology and telemedicine:
A feasibility study for the screening of cognitive decline

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Alla mia famiglia,

che ha sempre creduto in me.

KEYWORDS

Information and Communication Technologies (ICT)

Telemedicine

Cognitive Neuropsychology

Mild Cognitive Impairment (MCI)

Prospective Memory (PM)

ABSTRACT

Neurocognitive Disorders (NCDs) represent a public health priority for health systems worldwide. The lack of viable medication therapies for the more advanced phases of the continuum of NCDs has prompted researchers to concentrate on prodromal stages to delay or stop the progression of the disease. The term Mild Cognitive Impairment (MCI) refers to a transitional state between cognitive changes related to normal aging and dementia. Empirical evidence in the literature identifies Prospective Memory (PM) as an early cognitive function impaired in MCI individuals, concerning tasks with focal cues.

The health emergency due to the spread of the SARS-CoV-2 virus has highlighted the need for a restructuring of the national healthcare system with a focus on community medicine. This feasibility study aimed to test the possibility of assessing prospective memory using CRONO, a web app designed to allow rapid assessment of cognitive function, in some pharmacies in Parma configuring itself as hubs for telemedicine service rooted in the territory. Thirty-nine participants were recruited directly from pharmacies and underwent the CRONO test, and a neuropsychological assessment conducted in the Cognitive Psychology Laboratory of the University of Parma to compare the results of the two assessments.

The results, which are limited by the small sample size, demonstrate CRONO's good discriminative capabilities. In addition, the qualitative assessment of CRONO, carried out using the User Experience Questionnaire (USQ), revealed a very favorable overall evaluation on the part of the study participants. Even though they should only be viewed as preliminary, these findings set the stage for the design of future research projects that call for a bigger sample size.

ABSTRACT IN ITALIANO

I Disturbi Neurocognitivi (NCDs) rappresentano una priorità per la saluta pubblica per i sistemi sanitari di tutto il mondo. L'assenza di una cura farmacologica efficace per gli stadi più severi del continuum dei NCDs ha portato il mondo della ricerca a focalizzarsi sulle condizioni prodromiche al fine di ritardare o interrompere il decorso della malattia. Il termine *Mild Cognitive Impairment* (MCI) designa uno stato di transizione tra i cambiamenti cognitivi relati al normale invecchiamento e la demenza. Evidenze empiriche nella letteratura individuano nella Memoria Prospettica (MP) una funzione cognitiva precocemente intaccata negli individui MCI, con particolare riferimento ai task con cue focale.

L'emergenza sanitaria dovuta alla diffusione del virus SARS-CoV-2 ha messo alla luce la necessità di una ristrutturazione del sistema sanitario nazionale con particolare attenzione alla medicina del territorio. Questo studio di fattibilità ha voluto testare la possibilità di valutare la memoria prospettica attraverso l'utilizzo di CRONO, una web-app progettata per permettere una rapida valutazione della funzione cognitiva, in alcune farmacie di Parma configurandosi come hub per un servizio di teleneuropsicologia radicato sul territorio.

Trentanove partecipanti sono stati reclutati direttamente dalle farmacie e sottoposti al test CRONO e ad una valutazione neuropsicologica condotta nel Laboratorio di Psicologia Cognitiva dell'Università di Parma al fine di confrontare i risultati delle due valutazioni. I risultati, che soffrono di una bassa numerosità campionaria, mostrano una buona capacità discriminativa da parte di CRONO, inoltre la valutazione qualitativa di CRONO, eseguita tramite l'User Experience Questionnaire (USQ), ha fatto emergere un giudizio complessivo molto positivo da parte dei partecipanti allo studio. Questi risultati, anche se da considerare solo come preliminari, pongono le basi per lo sviluppo di studi futuri che dovranno coinvolgere un numero maggiore di partecipanti.

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Chapter 1

EHEALTH AND TELEMEDICINE

1.1 Digital age and eHealth

The digital age is a widespread phenomenon that permeates many aspects of contemporary life: Services, travel, entertainment, and business are just a few of the industries that have seen an increase in digitization. In the past 30 years, all aspects of human civilization have been impacted by the process of digital transformation that resulted from the development of digital technologies. *Information and Communication Technologies* (ICT) are one of the sectors most affected by digitalization. ICT refers to the collection of techniques and tools used to implement information transmission, reception, and processing systems. ICT has two components: The first is Information Technology (IT), which is information processing, and the other component is Communication (C), which means the transmission of information, but also involves technology (Gogia, 2019). The Internet, smartphones, radios, and televisions are some examples of the numerous everyday tools that fall under the umbrella of ICT. It could be argued that the very rapid changes in the ICT world encouraged first the World Health Organization (WHO) and then the world's health systems to focus on the concept of *eHealth*. The combination of digitization and health has given rise to eHealth, which has been defined as "the cost-effective and secure use of information and communications technologies in support of health and health-related fields, including health-care services, health surveillance, health literature, and health education, knowledge, and research" since 2005 when the World Health Assembly adopted resolution WHA58.28 (WHO, 2005, p.109). To enable healthcare institutions to use technology to provide services that are more in line with citizens' wants and expectations while improving the link between cost and quality of services, the healthcare sector has been brought into the digital age all over the world. The role of eHealth is to complement more traditional tools with more technological ones, to provide them to physicians

and patients to treat and protect health and well-being, to be achieved more efficiently and effectively. Making the health care system more efficient entails, for example, being able to reduce the time of medical procedures, generate more accurate diagnoses, provide more precision in medical procedures, and, finally, giving more information and more knowledge in disease prevention. Within the broader notion of eHealth is *telemedicine*, a simple and comprehensive definition of which is "the use of remote medical expertise".

1.2 Telemedicine

Telemedicine is the term used to describe clinical treatments provided over the distance between patient and provider. It includes diagnosis, observation, counsel, recommendations, reminders, education, intervention, and remote admissions. Clinical consultations by video conference, telementoring (supervising a procedure being performed by someone less experienced), digital monitoring with live feed or application combinations, and sending test reports for expert interpretation are some examples of different telemedicine applications. (Gogia, 2020). The expression was introduced in the 1970s by Thomas Bird to refer to the practice of medicine using an interactive multimedia communication system without the traditional physical interaction between the physician and the patient (Bird, 1975), in this definition the focus is on technology rather than the different contexts of use that is identified only with teleconsultation. The development of technology and the incorporation of ICT into medical practice more and more over the years, and the current definition is given by the WHO: "A composite term for health-related activities, service, and systems, carried out over a distance by means of information and communications technologies, for the purposes of global health promotion, disease, control, and health care, as well as education, management, and research for health." (WHO, 1998, p. 10). This definition succeeds in framing the correct complexity of the concept and covering the various fields of the use of telemedicine.

In the previous paragraph, we defined ICT, in the field of health care information processing follows four distinct processes known by the abbreviation of *DIKW* (Fig. 1). *Data* is a language of bits and bytes that are initially formed through input devices, stored in various locations as memory, and then sent or communicated. Data that is comprehensible to humans is *information*. Useful information becomes *knowledge*, and after that, gaining the advantages of knowledge is what is sometimes referred to as intelligence or wisdom. This can translate to proper action, which in the current context means better healthcare service.

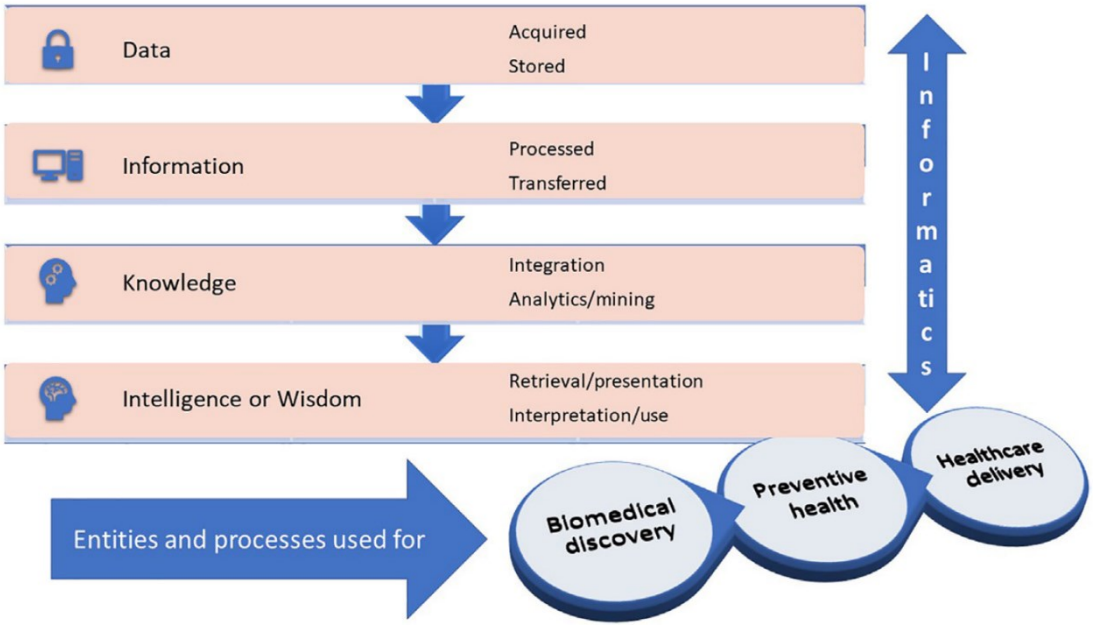


Figure 1 | Data flow in health IT systems. (Gogia, 2019, p.4)

The common thread in the definition of telemedicine, whichever one adopts, is that through it is possible to break down the distances between the actors involved because it is not the patient or the specialist who has to move, but the information, with the capability to manipulate very large amounts of data. This paradigm shift has been made possible by the refinement of ICT, which over time has made it possible to securely transmit and manage medical, clinical, and administrative information and data necessary for diagnosis, monitoring, and prevention of the patient's health status at home. The development of technologies opens new opportunities, which have been emphasized so far, but at the same time, some problems emerge on the ethical level, regarding the safety and efficacy of telemedicine applications, and privacy. Implying the storage, archiving, and transmission, including international, of sensitive data concerning the

health status of patients, as well as the remote collaboration of professionals providing their services, telemedicine poses the problem of protecting the privacy of patients, i.e., the proper treatment of data concerning their health status (Hale & Kvedar, 2014; Jalali et al., 2020). The issue of privacy is widely known to the public, and in the context of health care safeguarding the privacy of patients is one of the important aspects to be considered.

1.2.1. Purposes, types of intervention, and areas of application. Through increasing communication between the many health professionals engaged and patients, the development of telemedicine tools opens new prospects for improving health services while also enabling novel solutions to traditional medical problems. Equity of access to healthcare, increased care quality through guaranteeing continuity of treatment, improved efficacy, efficiency, appropriateness, cost containment and continuity of care and hospital-territory integration are the driving forces behind the development and implementation of telemedicine techniques and instruments.

Delving deeper telemedicine includes different health purposes:

1. Secondary prevention, aimed at people with diseases that need to be monitored over time.
2. Diagnosis, using telemedicine tools to take advantage of diagnostic information without moving the patient.
3. Care, to make therapeutic choices when the diagnostic picture is already clear.
4. Rehabilitation, that is, rehabilitative interventions carried out at the patient's home or another care facility.
5. Monitoring, for the management of the patient over time through an exchange of data between the patient and the staff responsible for interpreting them.

To better understand what services are available through remote medicine, it is necessary to divide it into three macro-categories: Specialty Telemedicine, Telehealth, and Teleassistance (see Fig. 2).

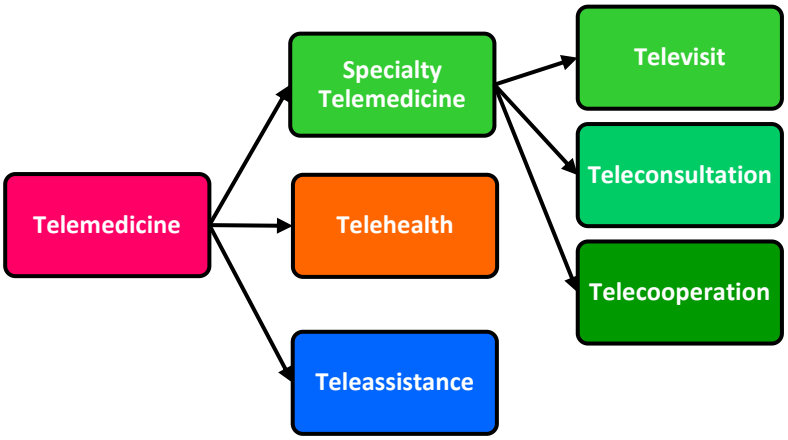


Figure 2 | Macro-categories of telemedicine and their respective ramifications.

Specialty Telemedicine refers to the provision of medical services within a specific discipline and can occur either between physician and patient or between different providers. According to this distinction, Specialty Telemedicine services can be carried out in the following ways: Televisit, teleconsultation, and telecooperation.

1. Televisit, which involves remote interaction between doctor and patient, following which drugs and treatments can be prescribed.
2. Teleconsultation, which consists of remote consultation between physicians and therefore does not involve the presence of the patient, even remotely.
3. Telecooperation health care, which occurs when a physician or other health care provider remotely assists another physician during a health care act, such as during an emergency rescue.

Telehealth sticks mainly to the primary care domain and applies mainly to chronic patients and concerns all systems that allow them to be assisted remotely in the stages of diagnosis, monitoring, and management of the disease itself. Patient *empowerment*, or increased patient involvement in the decision-making process for their care, is the topic of the latter aspect. The

many facets of the concept make it difficult to find a definition that is both all-encompassing and agreeable. Despite these clear classification challenges, the WHO tried at the first European Conference on Patient Empowerment, by the European Network on Patient Empowerment (ENOPE) in 2012 to offer a definition of empowerment that could be used by various writers. The WHO defines empowerment as a process that allows people to have more influence over choices and behaviors that have an impact on their health (Lancet, 2012). One of the characteristics of empowerment that different authors agree on is that patient participation is the focal element of this change (Castro et al., 2016). The second component of empowerment, according to guidelines imposed by the WHO, are patient skills, such as self-efficacy and health literacy (WHO, 2009). Bandura (2010) discusses and explains the idea of self-efficacy, defining it as confidence in one's capacity to plan and implement the course of action required to effectively handle the circumstances, we will meet to attain the desired objectives. Efficacy beliefs affect how people feel, think, find motivation, and behave. The idea of self-efficacy is valuable because people who have a high level of self-efficacy for a certain task are more likely to take on that work, are more driven, and typically execute more difficult tasks than people who have a low level of self-efficacy. Self-efficacy and empowerment are identified as concepts with very similar, sometimes overlapping qualities in a study of the literature. In a review of the literature, self-efficacy and empowerment are seen as concepts with very similar, partly overlapping characteristics. Several authors consider self-efficacy as an outcome of the empowerment process while others, including the WHO guidelines, propose that it is acquired during the process and as a necessary element for patient participation in decision-making, seen as the result of empowerment (Cerezo et al., 2016). It allows the patient to be taken care of by the physician, who is not only limited to monitoring the situation (Telemonitoring) but also supports him/her in the management of therapy. The relationship between Telemonitoring, Specialty Telemedicine, and Telehealth is schematized in Fig. 3.

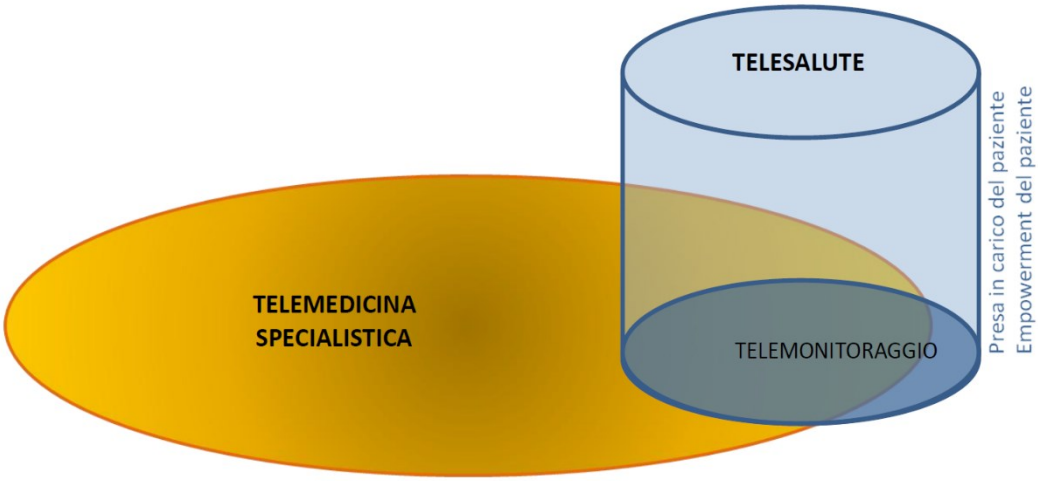


Figure 3 | Relationship between telemonitoring in telemedicine and telehealth. (Ministero della salute, 2012, p.12).

Lastly, teleassistance concerns the social welfare field and involves taking care of the patient at his or her home, through remote management involving, for example, the activation of 24-hour emergency services, alarm systems, and support calls from the facility providing the service.

1.3 The Italian telemedicine today

The development of telemedicine in Italy has experienced several significant historical turning points. Italy was one of the first nations in the world to test telemedicine, beginning in 1970 with the remote transmission of electrocardiograms. In particular, the "La Sapienza" Faculty of Medicine at the University of Rome conducted a telemedicine trial using a prototype Cardiophone to transmit biomedical data. Additionally, in 1976, the Marconi Foundation in Bologna began conducting research on switched telephone lines for tele-electrocardiography, allowing for the direct transfer of electrocardiograms from the hospital to the patient's home without the need for a cardiologist to personally visit the patient (Papi et al., 2000). The history of the institutionalization of telemedicine in Italy begins in 2007, on the 3rd Forum Risk Management in Healthcare, the Emilia-Romagna Region, with the support of the Ministry of

Health, established a National Observatory for the evaluation and monitoring of e-care applications. The Observatory was created to systematically analyze and catalog, and based on the latest studies in network science, e-care services, and to disseminate those that are recognized as good practices from the organizational, clinical-care, technological and economic points of view. The health emergency due to the spread of SARS-CoV-2, the new strain of coronavirus not previously identified in humans, from 2020 has led to the drafting of two important national documents regarding telemedicine:

- "National indications for the provision of telemedicine services" (Governo Italiano, 2020).
- "Indications for the provision of telerehabilitation services and services by the health professions" (Governo Italiano, 2021).

These documents became necessary due to the request for uniform directions throughout the country for the provision of remote services by the Ministry of Health and the Autonomous Regions and Provinces of Trento and Bolzano at the meeting of the New Health Information System (NSIS) Steering Committee held in the summer of 2020. These documents follow and complement, dwelling on outpatient activity and thus on the practical service delivery methods, the 2014 State-Regions Agreement on the document "Telemedicine - National Guidelines" (Governo Italiano, 2014) drafted in 2012 by the General Assembly of the Consiglio Superiore di Sanità to implement the European Communication COM-2008-689 (European Commission, 2008).

1.4 Neuropsychology and telemedicine

Teleneuropsychology (TeleNP) is broadly defined as the "application of audiovisual technologies to enable remote clinical encounters with patients to conduct neuropsychological (NP) assessments" (Bilder et al., 2020, p.648). Always because of the pandemic and social

distancing, it became clear the need to implement, in clinical practice, remote neuropsychological assessment in order not to delay neurocognitive disorder diagnoses and to provide continuity of care for patients already diagnosed. Even in a non-pandemic scenario, the remote modality would make it easier to reach people living in rural areas or with reduced mobility, affecting both clinical and research settings. When proposing an innovative service with different modes of delivery from the traditional ones, one of the most important aspects to consider is the opinion and acceptability of the same by the users**.** Parikh et al. in 2013 conducting a study of elderly people with and without cognitive impairment found that 98 percent of the total sample expressed overall acceptability of videoconference-based assessment. In addition, about 2/3 of the participants indicate no preference between traditional face-to-face testing and examination by TeleNP. In a recent review of Tele-neuropsychological assessment tools in Italy**,** Zanin and colleagues (2022) discovered suggestive results of the validity, reliability, and usability of brief screening instruments based on Internet, telephone, or videoconference for the assessment of cognitive and behavioral impairment. The authors continue by stating that these findings are consistent with other worldwide studies and contributions, particularly in TeleNP remotely administered instruments, which have demonstrated construct validity as well as criterion and ecological validity.

Chapter 2

THE CONTINUUM OF NEUROCOGNITIVE DISORDERS

Numerous advancements have been made in the fields of aging and neurodegenerative disorders during the past 20 years, with the crucial distinction between them on a continuum between normal and pathological aging (McDonald, 2017). Neurocognitive Disorders (NCDs) are characterized by a complicated cognitive decline and a chronic, progressive malfunction of the Central Nervous System (CNS), which is frequently accompanied by mood, behavior, and personality abnormalities. Researchers from all over the world are concentrating on the prodromal stages of this disease because of the disorder's progressive nature and the lack of efficacious medication treatment for the more severe forms. The most significant research was done on the Mild Cognitive Impairment (MCI), which is the prodromal stage of the development of major NCD or dementia, as will be detailed below. The state that precedes MCI is also the focus of more contemporary models, including Subjective Cognitive Disorder (SCD), which was invented by Jessen and colleagues (2014) to characterize those who report declining cognitive ability among elderly adults but are otherwise cognitively normal. Comprehensive disease models, like the one shown in Figure 4, have been developed as a result of the understanding that the clinical manifestations that characterize the most severe NCDs are the result of structural and functional changes in the CNS that happened many years earlier. Numerous studies have demonstrated that SCD is a significant risk factor for the development of MCI (Rönnlund et al., 2015) and severe dementia (Mitchell et al., 2014; Ohlhauser et al., 2018). The diagnosis of MCI is typically obtained in clinical practice after a neuropsychological assessment of a person exhibiting SCD, which emphasizes an actual cognitive failure, the lack of a real state of dementia, and intact independence in everyday activities. According to current management guidelines by Petersen et al. (2017), older adults with MCI have a tripled chance of developing Alzheimer's dementia within two to five years

compared to healthy older adults. The next several paragraphs will focus mostly on the MCI condition.

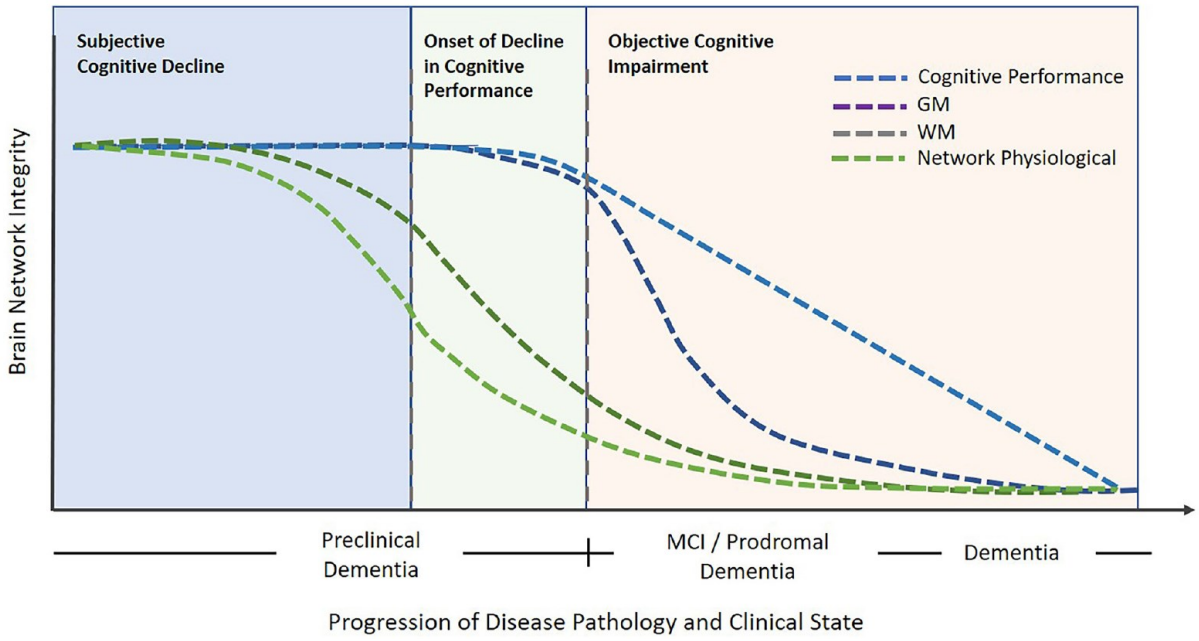


Figure 4 | Illustrative model contrasting cognitive loss related to progressive degeneration with brain network integrity. The blue dotted line depicts changes in cognitive function, the purple dotted line depicts changes in gray matter, the olive dotted line depicts changes in white matter, and the green dotted line depicts changes in the physiological state of the network (Fogel et al., 2021, p.9).

2.1 Mild Cognitive Impairment

MCI is a nosographic category useful to describe a broad spectrum of mild cognitive disorders. Because of the severity of the cognitive impairment and how it impacts the subject's daily living activities, they are referred to as having "moderate cognitive impairment" that prevents them from being labeled as dementia. About 80% of clinicians (Roberts et al., 2009) refer to the borderline period between normal biological decline associated with aging and the start of neurodegenerative illness as MCI, which is the most used name for the transitional condition between pathological aging and normal aging. Over time, various theories have been put forth to explain this neuropathological disorder (Petersen et al., 2014). It was developed by Reisberg and colleagues in the early 1980s to classify people with intermediate pathology based on their Global Deterioration Scale (GDS) scores (Reisberg et al., 1982). Petersen and colleagues first

used the term MCI in 1999 to describe individuals who were ranked in the middle of the cognitive performance range in a long-term Mayo Clinic study of aging and dementia in the community. At this early stage, the diagnosis of MCI was made in the presence of a memory disorder without impact on the functions of activities in daily living and with preservation of global cognitive function, in the absence of dementia, but with lower memory test scores than subjects of the same age and schooling (Petersen et al., 1999). The etiology of MCI was expanded at the Key Symposium in Stockholm in 2003, especially with the introduction of several clinical subtypes: amnestic (Amnestic MCI - aMCI), others involving multiple cognitive domains with or without memory impairment (Multiple-domain MCI) and, finally, the less common type with impairment of a single non-mnestic domain (Single Non-memory Domains MCI) (Petersen, 2004). The diagnostic algorithm for the diagnosis of MCI is shown in Figure 5.

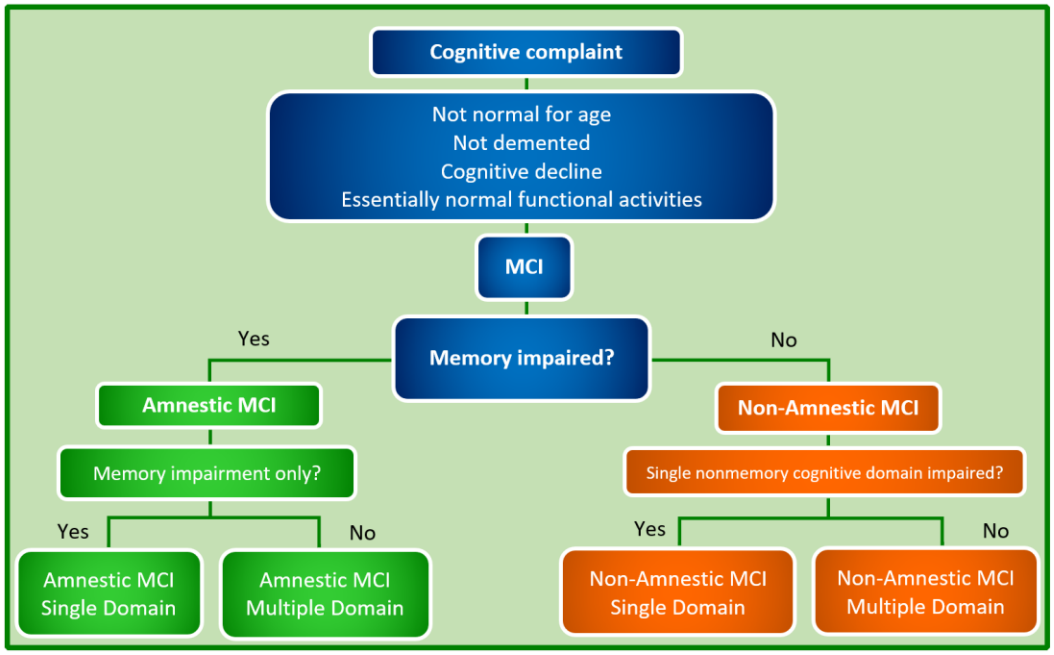


Figure 5 | Diagnostic algorithm for making subtypes diagnosis of mild cognitive impairment. (Restated from Petersen, 2004, p.190)

The Diagnostic and Statistical Manual for Mental Disorders (DSM-5) and the National Institute on Aging-Association Alzheimer's (NIA-AA) both employ the new, globally accepted criteria for the diagnosis of mild and major NCDs (APA, 2013).

2.2. Definitions in the framework of DSM-5

In the fifth version of the DSM, the American Psychiatric Association (APA) made some significant revisions to the diagnosis and nomenclature of NCDs. The most substantial adjustments are that the "cognitive disorder-not otherwise specified" category found in prior editions has been eliminated, the term "dementia" replaced by "major cognitive neurodisorder" was removed from the nosographic classification, a diagnosis of "mild neurocognitive disorder" (mNCD) was included and, finally, the concept of a continuum between normal cognitive function, mild and major NCDs is explicitly noted. (Sachdev et al., 2014; Simpson, 2014). In particular, the conceptualization of neurocognitive disorders (NCDs) provided by the DSM-5 emphasizes the biological-neural origin of symptoms and the acquired nature of deficits. This further distinguishes NCDs from neurodevelopmental disorders because the deficit is acquired over time, i.e., over the years the person has had a decline in cognitive function. The Neurocognitive Work Group, the group of authors that wrote the chapter on NCDs, recognized six cognitive domains as being representative of cognitive function. The presence of cognitive abnormalities in one or more of these domains characterizes the cluster of NCDs. The six key domains of cognitive function defined by DSM-5 are executive function, learning and memory, language, perceptual-motor function, complex attention, and social cognition (Fig. 6).

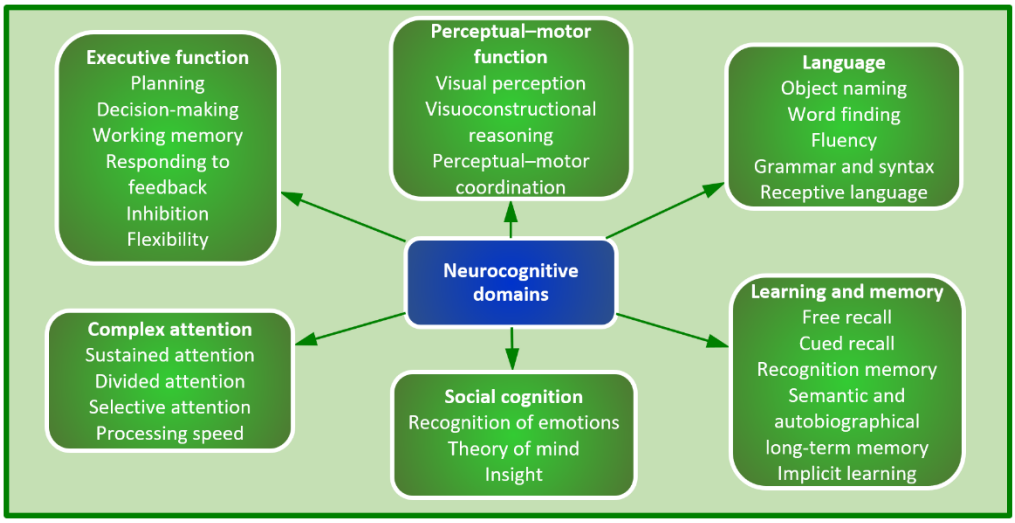


Figure 6 | Neurocognitive domains and their subdomains defined by DSM-5. (Restated from Sachdev et al., 2014, p. 3).

A syndromic diagnosis is formed at the initial step of the clinical process leading to the formulation of the diagnosis, and then potential cause elements are looked at to determine the etiology. Delirium, mild neurocognitive disorder, and major neurocognitive disorder are the three syndromes that make up the new DSM-5 terminology for neurocognitive disorders (Fig.7).

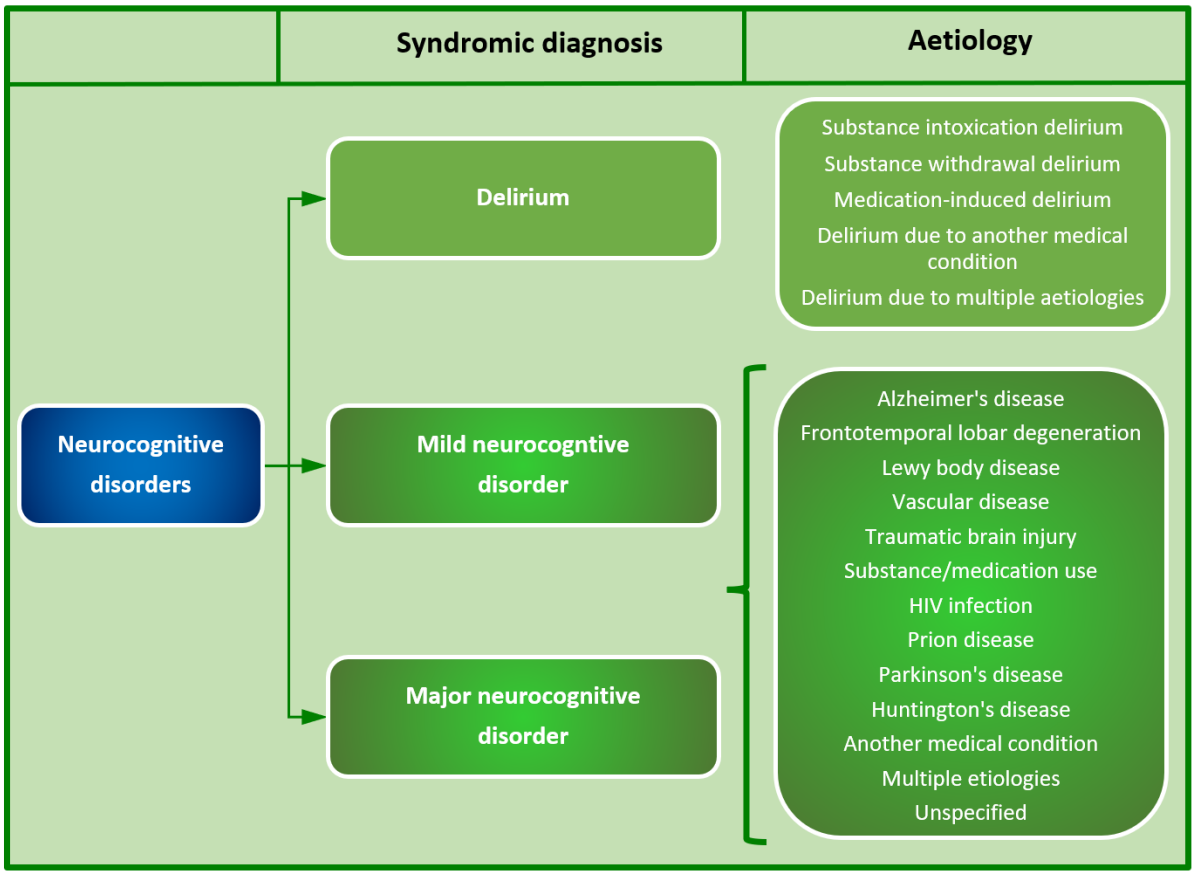


Figure 7 | DSM-5 diagnostic process for NCDs: First a diagnosis is made based on symptomatology. The second step is the aetiological one where mild and major NCDs share several possible causes.

2.2.1 Delirium. Delirium is primarily characterized by an individual's attention and consciousness being compromised. Delirium makes it difficult for a person to pay attention, focus on stimuli, or change their attention when it is needed. As a result, they have trouble answering queries from others and are quickly distracted. Delirium results in diminished awareness of oneself and others, as well as possible anxiety, depression, and emotional lability, which can occasionally cause a person to change abruptly and in an inappropriate manner

emotional state in front of others. Stupor, convulsions, coma state, and even death can result from delirium. This illness is uncommon in the general population, with its prevalence between 1-2%, and increases as people get older.

2.2.2 Mild and major neurocognitive disorders. In this broad category of neurocognitive disorders, there is a clear decline from a previous level of functioning in one or more of the key cognitive domains. According to Petersen et al. (2009) and Sachs-Ericsson & Blazer (2014), mNCD specifically corresponds to the diagnostic framework of MCI, while major NCD relates to the formerly nosographic category of dementia (Blazer, 2013; Petersen, 2016). Numerous investigations in the aging sector over the past 20 years have led to the requirement to define these two diagnostic constructs along a continuum of cognitive impairment from normal to severe impairment (Petersen et al., 2014). This goal is also realized in the DSM-5 through the parallelism of the diagnostic criteria for mild and major neurocognitive disorders, which, as shown in Box 1, differ primarily in the severity and functional impairment but not in the etiology or major criteria. In particular, "the criterion of independent functioning represents the key distinction between the mild and major neurocognitive disorders" (Sachdev et al., 2014, p. 4). The DSM-5 framework for NCDs is quite detailed and flexible, and it can vary on both quantitative and qualitative criteria, including clinical start and beginning symptoms, progression of development, cortical or subcortical involvement of the condition, biomarkers, and risk and prognostic factors. One of the main issues with the manual in this area is that no specific suggestions are made regarding the neuropsychological tests that should be used to gather the data about cognitive performance required to reach a diagnosis for the minor forms (mNCDs).

Mild neurocognitive disorder	Major neurocognitive disorder
A. Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on: 1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and 2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment. **B**. The cognitive deficits do not interfere with the capacity for independence in everyday activities (that is, complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required). **C**. The cognitive deficits do not occur exclusively in the context of a delirium. **D**. The cognitive deficits are not better explained by another mental disorder (for example, major depressive disorder or schizophrenia). Specify whether due to: • Alzheimer's disease • Frontotemporal lobar degeneration • Lewy body disease • Vascular disease • Traumatic brain injury • Substance/medication use • HIV infection • Prion disease • Parkinson's disease • Huntington's disease • Another medical condition • Multiple etiologies • Unspecified Specifiers • behavioral interaction.	**A**. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on: 1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and 2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment. **B**. The cognitive deficits interfere with independence in everyday activities (that is, at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications). **C**. The cognitive deficits do not occur exclusively in the context of a delirium. **D**. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia). Specify whether due to: • Alzheimer's disease • Frontotemporal lobar degeneration • Lewy body disease • Vascular disease • Traumatic brain injury • Substance/medication use • HIV infection • Prion disease • Parkinson's disease • Huntington's disease • Another medical condition • Multiple etiologies • Unspecified Specifiers • behavioral alteration • current severity (mild, moderate, severe).

Box 1 | Diagnostic criteria for mild and major NCDs from the DSM-5. (Restated from DSM-5, p. 602-606)

2.3 Diagnostic criteria: Neuropsychological tools, neuroimaging, and biomarkers

The diagnostic procedure can be separated into two primary stages: symptomatologic and aetiological, as demonstrated in the preceding section (see 2.2 par). The first stage can be completed utilizing neuropsychological tools, anamnestic record, and family member interviews; however, the second step needs additional analysis employing neuroimaging methods and biomarker identification. This section will provide a quick overview of each of these crucial components that make diagnosis possible.

2.3.1. Neuropsychological tools for MCI detection. Neuropsychology is the discipline that investigates the relations between brain processes and mechanisms on one hand, and cognition and behavioral control, on the other (Berlucchi, 2017). Neuropsychology employs the administration of standardized tests or batteries, along with behavioral observation and anamnestic recording, to gain a thorough assessment of the patient's cognitive-functional profile. This is frequently where a formal neuropsychological evaluation of a patient with a cognitive complaint starts. As a diagnostic technique for NCDs, neuropsychological evaluation provides unbiased input on deficits and potential cognitive impairments. The variety of available neuropsychological tests is not uniform; they can be classified according to domains and offer in-depth knowledge of one or more of those categories. The two basic types are tests for screening and specific domains evaluation. In clinical settings, among the most widely used screening tests are the Mini-Mental State Examination (MMSE; Folstein et al., 1975), the Frontal Assessment Battery (FAB; Dubois et al., 2000) and the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005). As was said in the previous section, the profile of MCI is quite disparate, and there may be multifunctional deficits that require a broad-spectrum test to be discovered. The main purpose of screening tests is to implement a systematic assessment of cognitive function. It is appropriate to deepen the neuropsychological assessment with tests

that continue to explore various cognitive functions in more detail once a screening test has evidenced a weak neuropsychological profile. In the context of NCDs in-depth assessment of mnestic abilities is the basic rule, examples of tests that allow a more complete assessment of memory are the following: Free and Cued Selective Reminding Test (FCSRT; Frasson et al., 2011), Rey Auditory Verbal Learning test (RAVLT; Rey, 1958), Babcock Test (Babcock, 1930), Digit Span Forward and Backward (Wechsler, 1987). The FCSRT has been very successful in recent years as it has been characterized as a specific test for detecting the amnestic subtype of MCI or mild dementia (Sarazin et al., 2010), in a recent PET study (Caffarra et al., 2016) it is noted that short-term memory (IFR) correlates with metabolism at the cingulate level bilaterally, while long-term memory (DFR) correlates with the anterior cingulate, but also with the midfrontal structures; finally, index of semantic cueing sensitivity (ICS) has a great correlation with a structure crucial for mnestic processes, that is the posterior cingulate (Fig. 8). This test is remarkable in that it places a lot of emphasis on the encoding phase of the stimuli, which makes it possible to rule out attentional deficits with a high degree of certainty and keeps the focus on mnestic abilities.

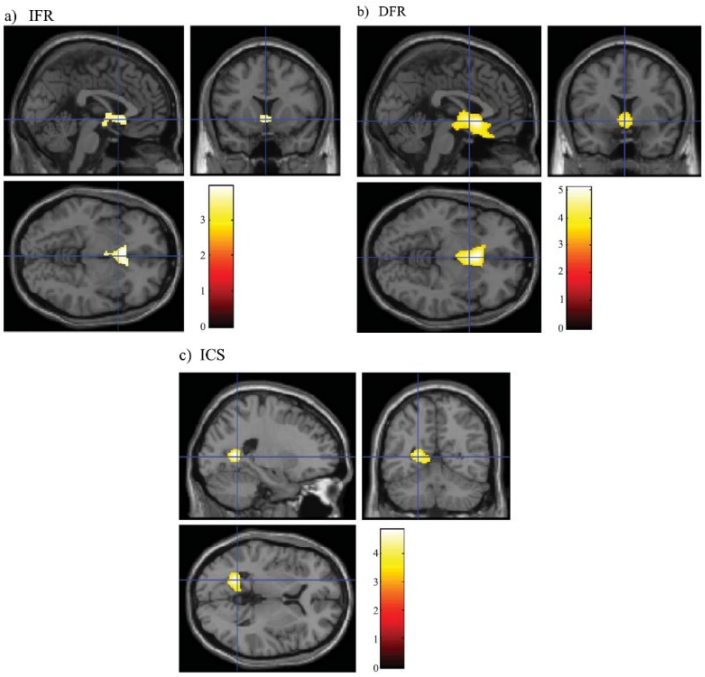


Figure 8 | Areas of significant correlation between brain metabolism and a) Immediate Free Recall (IFR); b) Delayed free recall (DFR); c) Index of semantic cueing sensitivity (ICS) (Caffarra et al., 2016, p.29).

Many additional instruments are used to define various cognitive abilities, including those related to attention, language, praxis, social cognition, and dedicated caregiver questionnaires that investigate the patient's level of autonomy in daily life and behavioral symptoms. These tools together allow for the creation of a comprehensive cognitive profile of the patient. Here will be discussed the findings of an intriguing meta-analysis by Brenton and colleagues (2018), who looked at the diagnostic reliability of various tests used in clinical practice for neuropsychological assessment. A diagnostic test is distinguished by its sensitivity, or the percentage of sick people that are correctly categorized, and specificity, or the percentage of healthy persons that are correctly classified:

$$\boldsymbol{Sensibility} = \frac{True\ positive}{Tot\ ill}$$

Probability of sick individual testing positive.

$$\boldsymbol{Specificity} = \frac{True\ negative}{Tot\ healthy}$$

Probability of healthy individual testing negative.

According to the authors of the study and the literature, it is desirable to put sensitivity first when designing a screening test because the purpose is to identify as many patients as possible while minimizing the number of false negative data. The meta-analysis results report that the Memory Alteration Test (M@T; Rami et al., 2007) is the most sensitive test among those examined, with a sensitivity of 0.951, higher than MoCA (0.812) and all other tests and has good specificity (0.84) equal to the MoCA. In contrast to MoCA, which was utilized in as many as 24 of the studies examined, the M@T is not commonly employed in clinical practice; in fact, it is reported that it was used in only 5 studies, although having a fairly significant number of participants. A final notable finding from this study is that the MMSE is by far the most extensively used test in clinical practice (46 studies), but it is also the least sensitive test (0.664), with a significant difference from the MoCA for the diagnosis of MCI.

2.3.2. MCI due to Alzheimer's Disease as an explanatory model. Alzheimer's Disease (AD) is the most common and best-known dementia and comprises up to 80 percent of all dementia

cases (Podcasy & Epperson, 2016). AD is characterized by three major brain abnormalities: First, the brain is atrophic with narrowed gyri, wider grooves, reduced brain weight, and expanded ventricles. Second, in autopsy sections of the brains of AD patients are present extracellular plaques of a dense material called amyloid, consisting of broad aggregations of fibrillar peptides organized into tangles. Third, damaged neurons that are still uninjured display cytoskeleton abnormalities as well. The accumulation of neurofibrillary skeins is the most significant of these abnormalities. Alzheimer himself first identified these morpho-structural changes in the brain in the early 20th century, and in recent years there has been a plethora of studies to find the biomarkers underpinning these changes early. The NIA-AA criteria for the specific classification of MCI resulted from AD in 2011 by outlining the biomarkers required for MCI discrimination. This clinical judgment mostly relies on two sets of biomarkers: Amyloid beta (Aβ) deposition indicators and neuronal injury. The valid indicators of Aβ deposition are concentration in cerebrospinal fluid Aβ42 (CSF Aβ42) and amyloid imaging by positron emission tomography (PET). While phosphorylated tau/tau in CSF, hippocampus volume or medial temporal atrophy, rate of brain atrophy, fluorodeoxyglucose (FDG) PET imaging, and SPECT perfusion imaging are all reliable indications of neural damage (Albert et al., 2011). The use of biomarkers is helpful for the early identification of individuals in the pre-clinical or prodromal stages of the disease (Jack, 2018).

2.3.3. Neurobiological alterations in MCI through neuroimaging. The common signs of MCI are modifications among various types to the neurological system. There have long been studies linking MCI participants' levels of performance to changes detectable with neuroimaging methods. It has been observed, for example, that the degree of white matter damage affects subjects' cognitive abilities (Petersen et al., 2005). In a study, Yan and colleagues (2013) found that individuals with MCI had impaired connectivity between the

precuneus/posterior cingulate cortex (PCC/PCC) and hippocampus as well as between the medial temporal gyrus, hippocampus, and fusiform gyrus (Fig. 9).

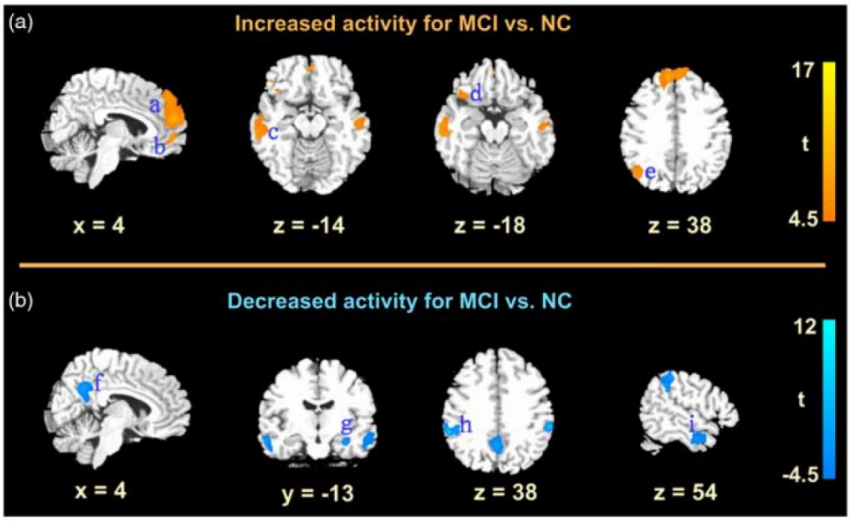


Figure 9 | Between-group maps of the default mode network for aMCI groups vs. normal controls (NC) (Yan et al., 2013, p.404).

Recent research has shown that individuals with MCI had a higher density of neurofibrillary tangles (NFTs) than individuals who are just experiencing age-related cognitive decline. In a different study, individuals were observed over time until death was first attributed to normal aging, then to MCI, and lastly to AD. At the basal nuclei, these individuals had neurofibrillary tangle levels that were noticeably higher than normal (Mesulam et al., 2004). Recent years have seen a rise in interest in neuroimaging studies employing a variety of methods in the field of MCI. In many of these investigations, participants with MCI had altered brain morphology including:

- Decrease in the subiculum's volume
- Decrease in the volume of the hippocampus
- Decrease in the volume of the CA1 region of the hippocampus
- Decrease in the entorhinal cortex's volume.

Additionally, it has been found that MCI is a good indicator of the development of AD disease since hippocampal and entorhinal cortex volume decline in MCI participants is more rapid than in those who are aging normally (deToledo-Morrell et al., 2004; Leandrou et al., 2020).

2.4 Context analysis: Aging, life extension, and cognitive decline

The significant increase in life expectancy has been the most significant accomplishment of the 20th century. As a result of significant improvements in health culture (such as the decrease in infant mortality, the introduction of vaccines and antibiotics, improved nutrition, and advances in the treatment and prevention of heart disease and strokes), developed countries have seen an average life expectancy increase from 50 years to 80 years (Crimmins, 2015). Aging is a process that can be defined as the precipitate of physiological, genetic, and molecular changes that accompany humans from birth to death (Weinert & Timiras, 2003). Age is the main risk factor for a variety of serious medical conditions, making increased longevity a double-edged sword: Just as our bodies change and degrade over time, the mind-brain unit and their functions also transform. In humans, as in other animals, physiological and anatomical changes that occur with increasing age contribute to physical and functional decline. Genetics, metabolism, immune system, and epigenetics are the four main biological domains identified by Cohen et al. (2019) as contributing factors to aging. These four main categories are widely affected by variations in both the body and the brain, which results in several impairments. Age-related declines in cognitive and functional abilities are among the most obvious signs of aging and one of the people's main worries (Cutler, 2015). Changes in brain structures, neural connectivity, and functionality occurring in aging are reflected in the cognitive functioning of individuals and can result in a progressive loss of independence, which as explained in the previous paragraphs is the main criterion for discriminating between a major and a mild NCD. Most people's quality of life is not significantly reduced by age-related cognitive changes; in fact, there is a great deal of interindividual variation and the potential of "aging successfully" (Anton et al., 2015, Rubin et al., 1998); however, the prevalence of neurocognitive disorders is increasing, which is the motivation that brings the World Health Organization (WHO) to recognize dementia as a public health priority (WHO, 2017). Several influential organizations,

such as the WHO and Alzheimer's Disease International (ADI; Gauthier et al., 2021), estimated 47 million dementia sufferers worldwide, a figure that is set to triple by 2050, resulting in social and human economic losses (Prince, 2017).

2.5 Prospective memory

Not all cognitive functions are equally affected by lifelong cognitive changes (Cohen et al., 2019). The difference between the active processing of new information based on external input or new associative processes (*fluid intelligence*) and the passive processing of new information based on acquired knowledge and basic skills (*crystallized intelligence*) is the basis of the dichotomy between crystallized and fluid intelligence (Cattel, 1963). The fact that fluid skills tend to deteriorate with age while crystallized capabilities tend to remain fairly stable is one of the most remarkable findings about how people's cognitive abilities change with age. This contradiction results from the fact that fluid functions frequently rely on executive functions, attention, working memory, processing speed, and process efficiency, all of which frequently deteriorate with aging. In contrast, basic cognitive functions, such as language and visual perception tend to deteriorate considerably less quickly. Prospective memory (PM) can be related to other cognitive abilities, and it is referable to the domain of fluid intelligence (Salthouse et al., 2004). PM is the capacity to recall carrying out predetermined intentions at the appropriate moment in the future (Brandimonte et al., 1996), it is a sophisticated cognitive process combining executive control, working memory, retrospective memory, and attentional processing (Kliegel et al., 2000). Suitable PM functioning is essential in all activities of daily life, from work activities (e.g., Remembering to attend a meeting; remembering to deliver documents), to social activities (e.g., Remembering an outing with friends; remembering to pick up one's children from school) and activities related to preserving one's health (e.g., take medicine at a specific time or after meals) (Beaver & Schmitter-Edgecombe, 2017).

Remembering to perform an action in the future is not a matter of course, but involves a complex mental plan called the prospective process, distinguished into five stages (Ellis, 1996):

1. Intention formation.
2. Retention interval.
3. Performance interval.
4. Performance of the intentional action.
5. Evaluation of the result.

Intention formation consists of deciding to do something and when and refers to the encoding of the content of future action, intention, and retrieval context. Retention interval refers to the time interval between intention formation and performance. The performance interval is the time during which the intention must be retrieved, which usually occurs when the appropriate context appears. Performance of the intentional action refers to the fact that something is to be done at a particular time. And finally, outcome evaluation refers to the comparison of the result of the action with the retrospective content. In a previous model, Brandimonte also added to these five main stages a sixth one in which one remembers having performed the action and therefore the action no longer must be repeated (cancellation phase). A PM task always has both a *retrospective component* (remembering what to do and when) and a *prospective component* (retrieving the action at the appropriate time). Assessment of PM is usually done through a test with a researcher or clinician. In these tests, the subject must perform the main task (an *ongoing task*) and at the same time must remember to perform an action at the appropriate time (*secondary task*). The secondary task can fall into one of two categories: event-based, where a specific event triggers the action's execution or it could be time-based, where a specific time or a set amount of time after the original timetable has passed needs to be remembered to realize the previously planned action.

2.5.1 Prospective Memory and MCI

A large proportion of individuals with amnestic MCI involve in AD at a rate of 38% per year (Maioli et al., 2007, Yaffe et al., 2006;). However, because memory deficits can be linked to a variety of memory-related tasks, it is not always easy to understand them and forecast potential developmental trajectories of the clinical condition. For example, attention deficit is prevalent in MCI: Attention represents one of the most important requirements for being able to encode any kind of information into memory. Alteration of this neurobiological function would result in a disruption in the subject's memory abilities. The direct impact of attentional difficulties, present in many patients diagnosed with MCI, can be observed in Working Memory (WM) tasks. According to a study by Saunders and Summers (2009), people with MCI who display dysfunctional attentional processes also struggle with WM tasks, language tasks that include semantics, and verbal and visual memory. Another crucial cognitive domain to consider is PM, particularly for the early detection of this kind of disease. One of the initial signs of MCI individuals who are at higher risk of developing AD is time-based prospective memory disorder (Spíndola et al., 2011). However, van den Berg et al. (2012) observed in their meta-analysis that MCI deficits were comparable in event-based and time-based activities. Compared to episodic memory problems, PM abnormalities are typically more severe and earlier in onset. This is most likely the case because they more accurately reflect the challenges associated with free recall, especially autonomously generated recall (Costa et al., 2011). The mechanism underpinning PM is complex and multi-faceted and entails both the spontaneous recall of delayed intents (episodic memory) based on an automatic-associative memory system and the strategic monitoring system (Arnold et al., 2015). Mesial temporal lobe regions, in particular the entorhinal cortex and the hippocampus which facilitate the spontaneous retrieval of encoded information (e.g., episodic memory), are affected by neuropathology in aMCI (Markesbery et al., 2006). Accordingly, various underlying neural deficits will hinder PM in

MCI (Hernandez et al., 2014); these include deficits in the automatic-associative system (which is necessary for the encoding and timely retrieval of delayed intentions), the strategic monitoring system (for flexibly switching attention between ongoing activities and the intended task), or most frequently an interaction of both systems (Kliegel et al., 2016). A major issue for clinicians in the context of MCI is that the purpose of neuropsychological assessment is often to contribute to the diagnosis of an inherent degenerative disease. Few PM tests have been included in neuropsychological assessments for MCI since there are currently few measures that provide full norms, especially in advanced age groups (Kinsella et al., 2018).

Chapter 3

FEASIBILITY STUDY

3.1 Purposes

The 2021 Alzheimer's Disease International (ADI) report estimates that worldwide 75% of people with dementia are undiagnosed, a percentage that can rise to 90% in low- and middle-income countries (Gauthier et al., 2021). The ADI's report, titled "Journey through the diagnosis of dementia" is largely oriented toward the analysis and description of the difficulties of diagnosis formulation processes in the world. Given these premises, it follows that it is desirable to promote screening programs based on sufficiently sensitive assessment tools and preventive programs that consider dementia risk factors.

The present study has two main aims: first, to assess the feasibility of a locally rooted telemonitoring service for cognitive decline; second, to place itself in continuity with the results produced by a broader investigation conducted by the Cognitive Psychology Laboratory of the Department of Medicine and Surgery of the University of Parma, whose main objective is the validation of CRONO, a software designed to rapidly investigate cognitive function.

The first goal was evaluated with the involvement of some pharmacies in the city of Parma in promoting a memory assessment service and through the analysis of the User Experience (UX) in using CRONO, of the study participants. The second was conducted through an analysis of the results obtained from a classical neuropsychological assessment compared with those identified by the CRONO software.

3.2 Previous results

A previous study investigated the diagnostic accuracy of CRONO in detecting cognitive impairment in a sample of 55 subjects, who performed a similar protocol, but with some important differences, to the one presented in this study. Specifically, CRONO consists of five

different tasks (*updating*, *inhibition*, *shifting*, *bisyllabic words,* and *prose memory*) investigating different cognitive components, and only the last two tasks investigate PM. In the previous study, subjects performed all five tasks, but the subsequent statistical analysis looked only at the results obtained from the two prospective tasks. In contrast, the battery of tests used to perform the neuropsychological assessment was the same as that used in this study and will be analyzed next. A further difference from the previous study also lies in the fact that the CRONO test in this work was performed in the pharmacies involved in the research project, whereas in the previous one it was carried out in the Cognitive Psychology Laboratory of the University of Parma. The results of the logistic regression model performed to identify the diagnostic accuracy of CRONO in the previous study is shown in Table 1.

Predittore	β	*S.E* β	*Wald's* x^2	*DF*	*pvalue*	*OR*	*95%CI*
Crono	*0.64*	*0.29*	*0.17*	*1*	*0.02*	*1.90*	*0.11 - 1.26*

Table 1 | Results derived from the application of the logistic model; the angular coefficient (β), the standard error associated with it (S.E β), the value of the quantile x2 (Wald's x2), the degrees of freedom moving from the null model to the model with predictor (DF), the p-value (significant), the odds ratio related to the angular coefficient (OR) and, finally, the confidence interval related to it, attested at a 95% level of likelihood, are reported, respectively.

Thus, the findings of the prior investigation led to the conclusion that CRONO had a low predictive capacity in identifying cognitive impairment.

3.3. Description of the feasibility study

The research project concerning this study is an attempt at locally rooted telemonitoring regarding cognitive impairment screening involving some pharmacies as service delivery sites. The choice of pharmacies is due to cultural, strategic, and contextual factors: During the pandemic, even among the different difficulties due to the contingency, a large part of the citizens perceived the pharmacy as a "safe" place and where to find the useful information to

face the health emergency. National pharmacies have contributed greatly to the important campaign of infection screening through the swab service going to make up for the difficulties of large hospital centers. The Italian pharmacy world has embraced the difficulties of the National Health System (NHS) and has firstly enabled the monitoring of the spread of COVID-19 disease and secondly made the vaccination service available to the population.

The previous study emphasized the need to improve the software's correctness, clarity, and usability because the task instructions were not easy for users to understand. Therefore, focus groups were conducted with the Department of Computer Science at the University of Bologna to improve the usability of CRONO by going to implement a *user-based user experience*. The following is a summary of the new features of CRONO compared to the previous study:

1. Introduction of images to enhance the user experience, such as the one in Figure 10.
2. Implementation of a serious-game approach: this type is highly relied upon in the literature precisely to enhance the user experience. In the version of CRONO used in this study, the serious-game approach finds its explication primarily in the terminology used in the description of task instructions, i.e., *gamification*, rather than in the use of the software. The desire to implement more of the serious-game approach in CRONO will be described in the conclusions.
3. Lexicon and clarity of exposition, there has been a move to simplify and improve the effectiveness of instructions and a shift from 3rd person to 2nd person to make the software more colloquial and understandable.
4. Changes in the operationalization of prospective memory tasks (e.g., it was decided to change the key to perform the prospective task from "spacebar" to "alt") that could cause user confusion in the previous version.

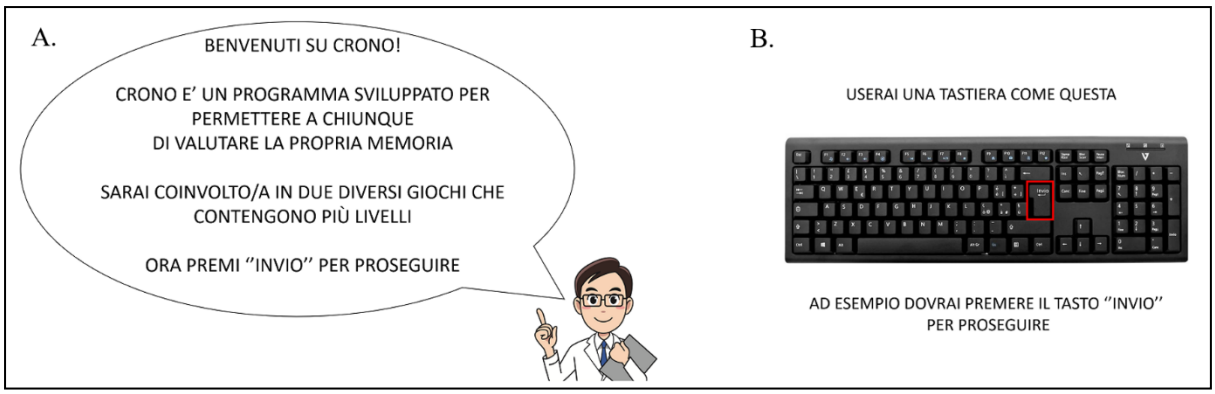


Figure 10 | New graphical interface of the CRONO's first page (A) and instructions for using the keyboard

After making changes to the software, the pharmacies to be involved in the study have been identified in collaboration with FarmaiTech, a company that prevents digital services to pharmacies. After exposing the research design and showing the software to the pharmacy owners and employees, recruitment of the subjects was carried out, which, in this study, was all given by the pharmacies themselves. To facilitate the publicizing of the new memory assessment service, posters and leaflets were created (See Appendix - Section 1).

3.4 Methods and Material

3.4.1. Participants and sample description. Forty-four subjects were recruited to participate in the study, they were recruited directly and independently by pharmacies that took part in the study and evaluated on five days, called "CRONO DAY", between June and September 2022. Of the forty-four subjects recruited thirty-nine participated in both phases of the trial. The final sample thus consists of 39 adults (74.36% women) between 47 and 83 years old (M = 62.95 years, SD = 8.62 years). In terms of educational level, the sample consists of 9 college graduates, 19 high school graduates, and 11 with middle school diplomas. All participants were volunteers and did not receive any monetary reward.

3.4.2. Ethics. The Area Vasta Emilia Nord (AVEN) ethics committee received the study research protocol for review and approval; the latter occurred on June 9, 2020. The study was

carried out in accordance with the guidelines for research on human subjects outlined in the Declaration of Helsinki, created by the World Medical Association (WMA). All subjects were informed about the purpose of the research, the instruments used, and the procedure for administering them and gave their written consent, knowing that they could withdraw from the investigation at any time.

3.4.3. CRONO. CRONO is a web application, or *web-app*, developed by the Department of Computer Science at the University of Bologna in collaboration with Prof. Olimpia Pino, head of the Cognitive Psychology Laboratory of the Department of Medicine at the University of Parma. The main advantage of a web-app is portability, as unlike software programs that run locally on the Operating System (OS) it runs in a web browser, so an Internet connection is sufficient to access it. When programming an application, it is necessary to think about three main components: The database, software infrastructure, and the web server. CRONO is implemented in a database that takes advantage of SQLite technology, a library written in the C language, which implements an *ACID* (Atomicity, Consistency, Isolation, Durability) type of *Database Management System* (DBMS), this ensures maximum reliability of operations performed on the data. As for the software infrastructure, the use of Django (www.djangoproject.com) a free and open-source web application framework written in Python was chosen. As for the CRONO web server, it is supported on Nginx (www.nginx.com) one of the most efficient and versatile open-source web servers. CRONO consists of five different tasks aimed at assessing different cognitive domains, such as controlled attention, working memory, and, prospective memory: Updating, shifting, inhibition, bisyllabic word test, and prose memory test. In this experiment only the last two tasks were used, those aimed at evaluating PM, which will now be explained.

1. *Prose memory test*: The test consists of 4 trials, each of which involves the presentation of an excerpt that participants must read carefully and, at the end of each trial, answer a comprehension question (an ongoing task). This test is aimed at assessing PM activity as a function of cue focality, which can be focal or non-focal. Specifically, this test is an event-based mode test: The subject must press the "Alt" at the appearance of a given target during the performance of the ongoing task. During the performance of the task, is necessary to monitor the presence of specific targets within the passage, which can be words (focal cue) or categories (non-focal cue). This test requires mnestic retention of the details of the excerpt, in conjunction with an attentional control process aimed at prospective cue detection.
2. *Bisyllabic word test*: This test consists of 6 trials within which a list of words is presented in varying numbers (ranging from a minimum of one to a maximum of seven), and at the end of each presentation, the participant must perform an immediate recall of the presented set and type in all displayed items (an ongoing task). For PM assessment during the immediate recall task, the subject is asked to press "Alt" whenever a particular item appears within the proposed list. Also in this test, the target can be a specific word (focal cue) or a category (non-focal cue).

3.4.4. User experience and workload. The previous study had highlighted several shortcomings from the usability point of view of CRONO so several changes were made to improve the user experience. When designing software, it is very important to consider user experience (UX) as a construct to evaluate its merits and flaws. The *User Experience Questionnaire* (UEQ) was chosen to evaluate the UX of CRONO. Qualitative analysis of the software was deepened by assessing workload through the NASA-Task Load Index (NASA-TLX), a subjective workload measurement tool. The NASA-TLX is one of the most widely used instruments in the literature

and is based on the operator's assessment of the workload experienced after the execution of a task and assumes that the phenomenal experience of the effort expended is a reliable indicator of workload. In this test, the workload is composed of six subscales that contribute to its definition: *Mental Demand*, *Physical Demand*, *Temporal Demand*, *Performance*, *Effort,* and *Frustration Level*. The description of the scales is an integral part of the test; in fact, they must be reported in full in the administration, and are shown below:

- *Mental demand*: How much mental and perceptual activity was required (e.g., thinking, deciding, calculating, remembering, looking, searching, etc.)? Was the task easy or demanding, simple or complex, exacting or forgiving?
- *Physical demand*: How much physical activity was required (e.g. pushing, pulling, turning, controlling, activating, etc.)? Was the task easy or demanding, slow or brisk, slack or strenuous, restful or laborious?
- *Temporal demand*: How much time pressure did you feel due to the rate or pace at which the tasks or task elements occurred? Was the pace slow and leisurely or rapid?
- *Performance:* How successful do you think you were in accomplishing the goals of the task set by the experimenter (or yourself)? How satisfied were you with your performance in accomplishing these goals?
- *Effort*: How hard did you have to work (mentally and physically) to accomplish your level of performance?
- *Frustration Level*: How insecure, discouraged, irritated, stressed and annoyed versus secure, gratified, content, relaxed and complacent did you feel during the task? (Hart & Staveland, 1988, p.32)

The version used is the one provided by Bracco & Chiorri (2006) who were directly contacted and provided their version of NASA-TLX. The two questionnaires were completed by 51

people including the experimental subjects and staff from the pharmacies that participated in the project.

3.4.5 Neuropsychological assessment. The battery of standardized tests used in the assessment included, in this order:

1. *Free and Cued Selective Reminding Test* (FCSRT; Frasson et al., 2011), a tool for the in-depth study of memory function aimed at detecting the subject's capacity of immediate and deferred recall and useful in identifying the prodromal stages of more major forms of cognitive impairment.
2. *Digit Span* (Monaco et al., 2015), is one of the most used tests for assessing *working memory*.
3. *Montreal Cognitive Assessment* (MoCA; Aiello et al., 2021), a tool designed for rapid screening of mild cognitive impairment widely used in clinical practice and with good diagnostic accuracy
4. *Prose memory test: Babcock's short story* (Spinnler & Tognoni, 1987), aimed at assessing the capacity for immediate and delayed episodic reenactment.
5. *Mini-Mental State Examination* (MMSE; Foderaro et al., 2022), a multi-domain screening test extensively used in clinical practice because of its rapidity of performance and reproducibility, but it has poor diagnostic accuracy.
6. *Rey Auditory Verbal Learning Test* (RAVLT; Carlesimo et al., 1996), one of the most broadly used tests in clinical protocols for assessing learning and verbal long-term memory of new information
7. *Milan Overall Dementia Assessment* (MODA, Subtest Constructive Apraxia; Arrigoni & De Renzi, 1964), aimed at the detection of constructive apraxia through the replication of a three two-dimensional figure models

8. *Corsi Block Tapping Test* (Monaco et al., 2015), aimed at assessing visuospatial memory, is a fairly complex test in that it involves a motor planning component that is distinct from visuospatial mnestic processes.

3.5 Results

The evaluation of CRONO's user experience (UX) by USQ and NASA-TLX will be done first, followed by a comparison of CRONO's diagnostic accuracy to that of MoCA and MMSE.

3.5.1. UX CRONO. The USQ was filled out by 51 people, including subjects who did not complete the experimental process and pharmacists who tried the test themselves. Nine individuals were removed because their responses did not follow the parameters provided by the questionnaire's creators. Forty-two participants make up the final USQ sample result. The overall results of CRONO UEQ scale are depicted in Table 2.

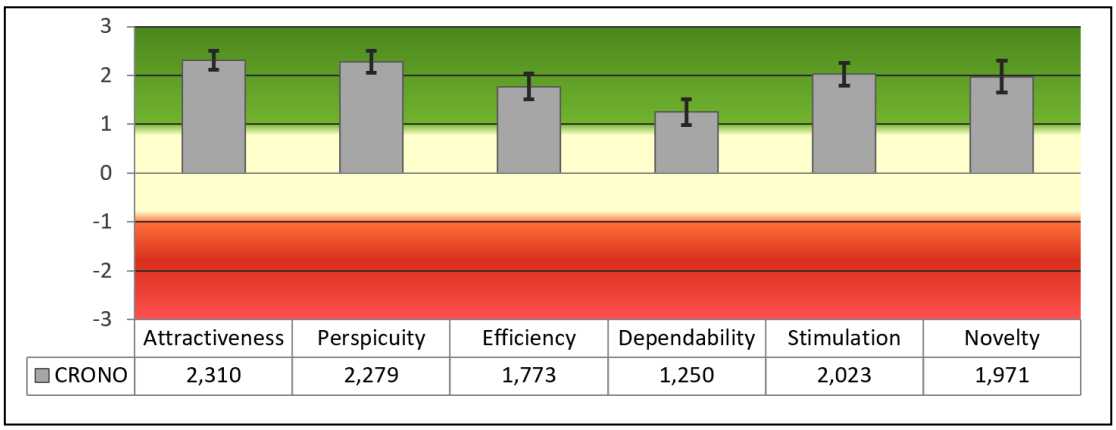


Table 2 | Average UEQ scale values of CRONO. *Attractiveness:* Overall impression of the product. Do users like or dislike the product? *Perspicuity:* Is it easy to get familiar with the product? Is it easy to learn how to use the product? *Efficiency:* Can users solve their tasks without unnecessary effort? *Dependability:* Does the user feel in control of the interaction? *Stimulation:* Is it exciting and motivating to use the product? *Novelty:* Is the product innovative and creative? Does the product catch the interest of users? (Schrepp et al., 2014, p.385)

As can be seen from the graph, the overall rating of CRONO falls within the green band of the graph, the one referring to a positive rating. However, the internal consistency of the scales as determined by the Alpha-Coefficient is one of the most crucial factors to consider while using

this questionnaire (Cronbach, 1951, Schrepp et al., 2014). Table 3 contains the alpha coefficients and associated confidence ranges.

Scale	Alpha	Conf. Int. Alpha (5%)
Attractiveness	.82	.65 - .87
Perspicuity	.71	.41 - .78
Efficiency	.41	.19 - .70
Dependability	.26	-.25 - .54
Stimulation	.54	.55 - .84
Novelty	.67	.62 - .86

Table 3 | Alpha coefficients and relative confidence intervals of the six dimensions measured by CRONO to define UX.

The values of several scales are severely insufficient, even though some individuals were removed due to the low consistency of their responses, and on scales where an acceptable level of internal consistency is obtained, the confidence intervals are excessively wide. According to the authors of the questionnaire, such low values may be mainly due to low numerosity or lack of understanding of one or more items that constitute a scale.

One of the items that constitute the *Dependability* scale is item n.8, namely *unpredictable – predictable* which, as shown in Fig.11 is skewed toward unpredictable. The frequency of the respondent's responses to the various questions is another intriguing aspect of this graph. The graph shows that item n.8 is the only dimension with a negative connotation to have greater rates. Unpredictability is defined as having a negative value by the dichotomy of item n.8 on the questionnaire scales, but in the context of this study, being unexpected has a positive connotation because it shows that CRONO interaction necessitates a particular amount of attention.

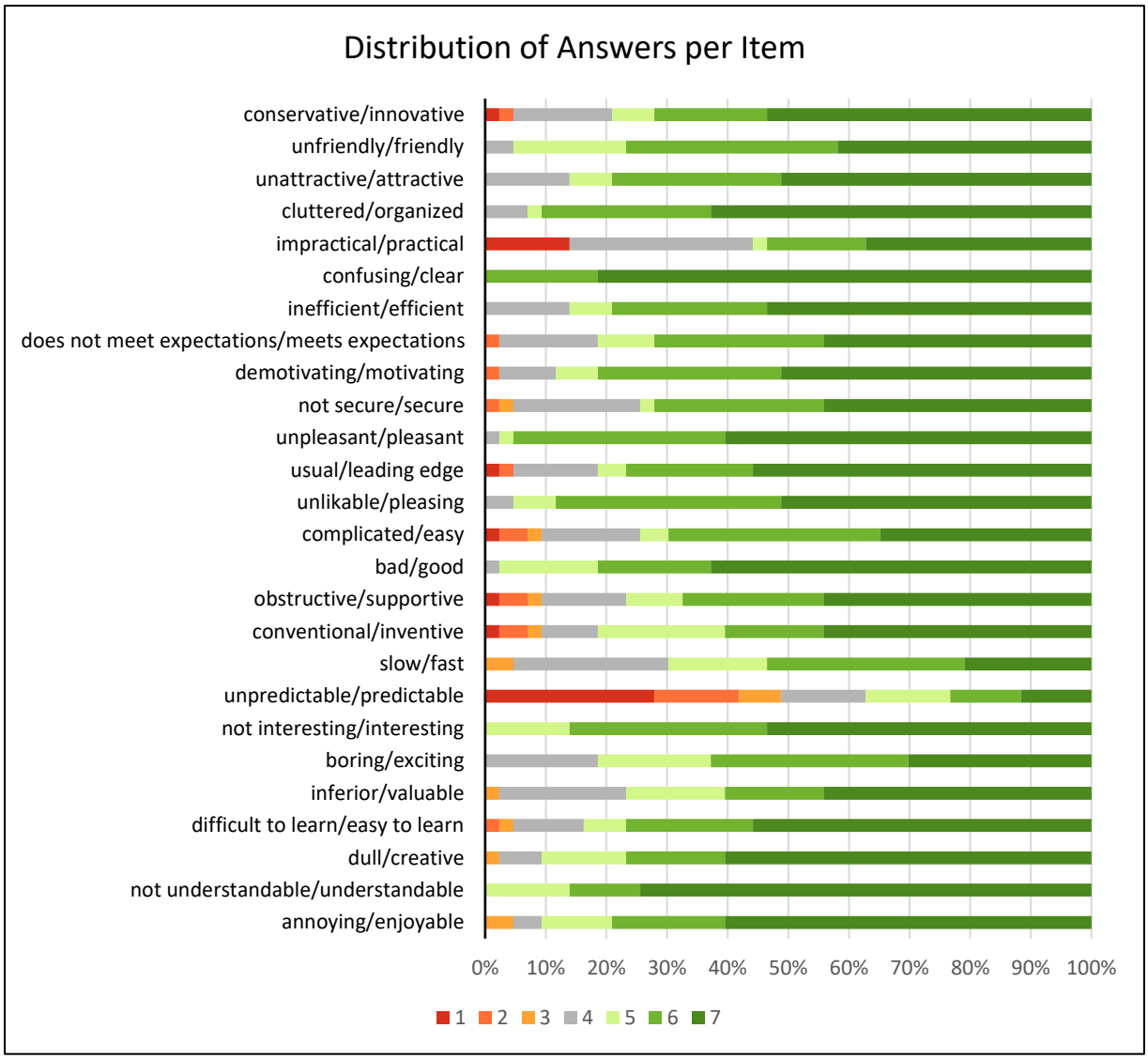


Figure 11 | Distribution of answers to the single items. This chart also represents the 26 items of contrasting characteristics that make up the USQ.

The USQ allows to compare the results obtained from your product with a database containing 468 different studies, with a total sample size of 21175 people. Figure 12 displays the graph comparing the CRONO Benchmark to the information in this database.

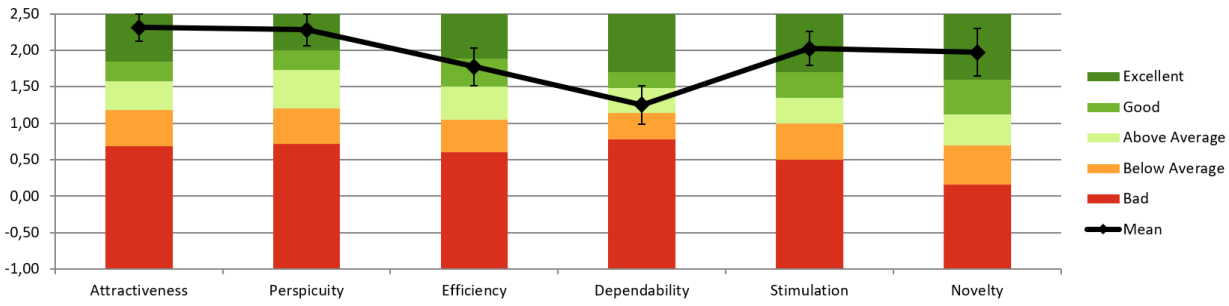
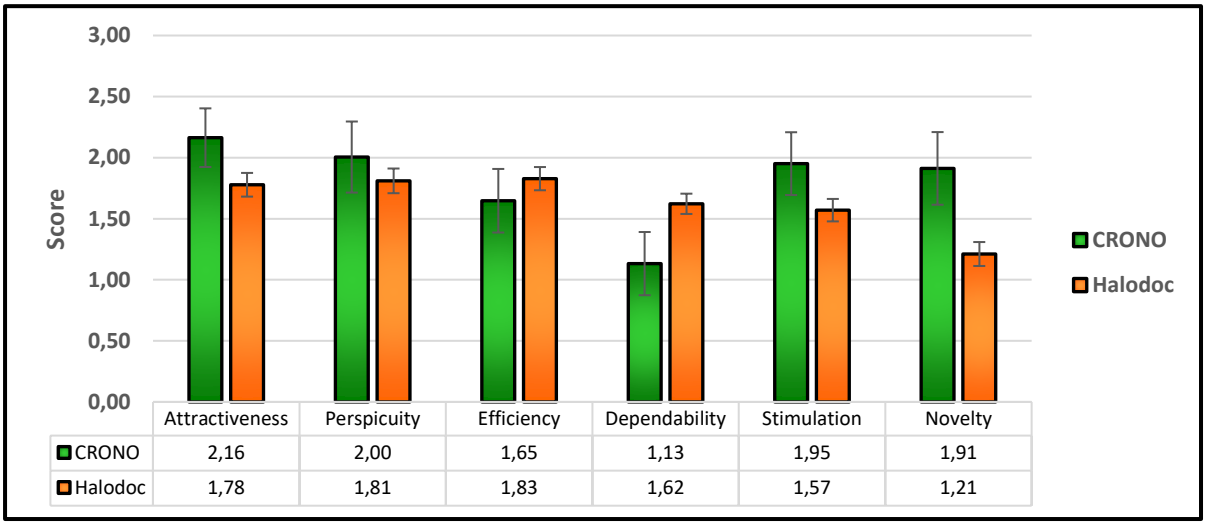


Figure 12 | UEQ benchmark diagram on CRONO.

With an auxiliary tool offered by the test authors is possible to swiftly compare two products, or two versions of the same product, to see the consequences of upgrades made. Few studies have utilized the USQ to evaluate their product in the context of telemedicine; other questionnaires are mostly used in telemedicine (Hajesmaeel-Gohari & Bahaadinbeigy, 2021). However, a 2021 study made available the scores of the six USQ scales that were used to compare with those obtained by CRONO. Table 4 shows the CRONO and Halodoc application for smartphone scores from another study that used the UEQ to evaluate the usability of a smart health application (Kushendriawan et al., 2021).



	Attractiveness	Perspicuity	Efficiency	Dependability	Stimulation	Novelty
CRONO	2,16	2,00	1,65	1,13	1,95	1,91
Halodoc	1,78	1,81	1,83	1,62	1,57	1,21

Table 4 | Comparison CRONO and Halodoc. (C.I. of the Halodoc app values are not real matches; they are placed randomly).

This comparison is useful for understanding the findings that belong to CRONO and the rates produced are consistent with the results obtained by Kushendriawan's sample in his study, as seen from the graph. For CRONO, the small sample size led to very broad confidence intervals; unfortunately, they weren't accessible for Halodoc. These two factors restricted the analysis to the qualitative observation of the comparison; in this initial investigation, it was crucial to determine whether the subjects had a proper understanding of the questionnaire. Finding comparable outcomes when utilizing the same questionnaire could show that the data is reliable. These results, although only preliminary, are highly encouraging and show that CRONO has quite a good UX.

At the end of the test with CRONO, in addition to the UEQ, the NASA-Task Load Index (NASA-TLX) was also administered to measure the perceived workload while performing the test. Table 5 shows the NASA-TLX scale results. In general, it is clear from the graph that mental demand, especially when compared to temporal and physical demand, is the main factor contributing to the workload when using CRONO. In addition, there is a positive perception of one's performance and the effort required to complete the test is also quite high.

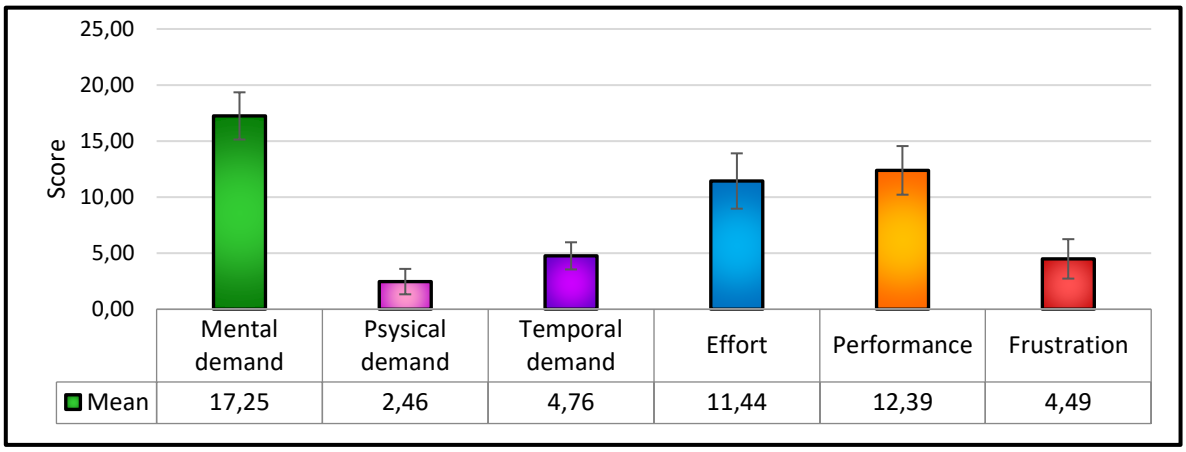


Table 5 | Mean NASA-TLX scales of CRONO.

This test is used in a variety of contexts even very different from each other, so it is not easy to interpret its results, an attempt is offered by Grier's (2015) meta-analysis. Specifically, the author reports the Cumulative Frequency Distributions of NASA-TLX Global Workload Scores by Task Type, the average score of two types of tasks ("*Cognitive tasks*" and "*Computer Activities*") were used to compare them with the CRONO scores. The results of this comparison are shown in Table 6.

	Min	**25%**	**50%**	**75%**	**Max**
CRONO	11.67	33.50	52.33	64.00	100.00
Sample-1	10.27	29.50	50.00	57.33	71.45

Table 6 | Cumulative Frequency Distributions of NASA-TLX Global Workload Scores by CRONO and Sample-1, the average of Cognitive tasks and Computer Activities.

The findings of this latest analysis make it possible to state that the workload associated with CRONO is consistent with that found in several studies in which workload was investigated in activities like those performed by subjects using CRONO. In particular, the middle range of scores, the one contemplating 25-75%, is very similar.

3.5.2. Neuropsychological assessment. After performing the first part of the study in the pharmacy using CRONO, subjects scheduled an appointment and performed the classical neuropsychological assessment in the Cognitive Psychology Laboratory. Following the neuropsychological assessment obtained from the battery, medical history, and behavioral observations the subjects were classified into "impaired" and "not impaired". Table 7 shows the mean scores and standard deviations of the two groups.

Not impaired (N=31)			Impaired (N=8)		
	Mean	**SD**		**Mean**	**SD**
MoCA	24.39	1.8	**MoCA**	19.05	2.0
MMSE	28.65	1.07	**MMSE**	26.45	1.86
FCSRT (IFR)	30.87	2.19	**FCSRT (IFR)**	29.74	1.72
FCSRT (DFR)	10.80	.99	**FCSRT (DFR)**	10.54	1.51
Digit span forward	6.07	.62	**Digit span forward**	5.24	.78
Digit span backward	4.56	1.12	**Digit span backward**	3.94	.77
Babcock	12.67	2.09	**Babcock**	7.97	1.98
REY (RI)	49.54	9.32	**REY (RI)**	38.72	19.61
REY (RD)	11.14	3.05	**REY (RD)**	8.70	4.48
Corsi span forward	5.16	.97	**Corsi span forward**	5.24	.80
Corsi span backward	4.94	1.04	**Corsi span backward**	4.43	1.10

Table 7 | Mean scores and relative standard deviations to neuropsychological assessment tests in the two groups.

The outcome of the neuropsychological battery was the crucial diagnostic element in defining the subjects into "impaired" and "nonimpaired", however, membership in the two groups was defined by the history collection, analyzing risk and protective factors, and by behavioral observations.

The software's ability to predict whether participants belonged to one or the other group was assessed using a logistic regression-based model. Specifically, the results of the two prospective CRONO tasks' focal tests for "Prose Memory" and "Bisyllabic Words" were considered to make the evaluation: A maximum of 5 points could be earned by summing the results of the two prospective tests (2 points from the "Prose Memory" task and 3 points from the "Bisyllabic Words" task). The prospective memory scores obtained from the CRONO tasks by the two groups and their standard deviations are presented in Table 8.

Not impaired (N=31)		
	Mean	**SD**
CRONO Score	4.03	0.91

Impaired (N=8)		
	Mean	**SD**
CRONO Score	2.88	0.64

Table 8 | Mean scores and relative standard deviations to CRONO tasks in the two groups.

In addition, a logistic regression model was also applied for the scores of the MoCA and MMSE, the other two screening tests in the neuropsychological battery used, to have greater clarity in the interpretation of the results. The results derived from logistic regressions are presented in Table 9.

Predictor	**β**	**S.E β**	**Wald's z**	**p-value**	**OR**	**95% CI**	**Pseudo R^2**
CRONO	1.53	.59	2.577	.001	4.60	.52 – 2.93	.397
MMSE	1.2	.47	2.564	.01	3.33	.45 – 2.33	.486

Table 9 | Results derived from the application of the logistic models. The regression slope (β), the standard error associated with it (S.E β), the value of the quantile z (Wald's test), the p-value, the odds ratio related to the slope (OR) and the OR 95% confidence interval and, finally, the Pseudo R^2 (McKelvev Zavoina).

The logistic regression model was significant for both CRONO and MMSE. Specifically, for each additional point at CRONO the probability of belonging to the non-compromised group increases by 4.60, while for MMSE this statistic is 3.33. The McKelvey Zavoina fit index

reports the proportion of the total variability of the outcome that is accounted for by the model and is .397 for the model with CRONO as predictor and .486 for the MMSE. The parameters of the logistic regression model applied to the MoCA scores were not reported because its prediction was almost perfectly, with almost complete separation between impaired and not-impaired scores, in which only one subject belonging to the compromised group has a score higher than the minimum of the non-compromised group and no subject from the non-compromised group has scores in common from the compromised group.

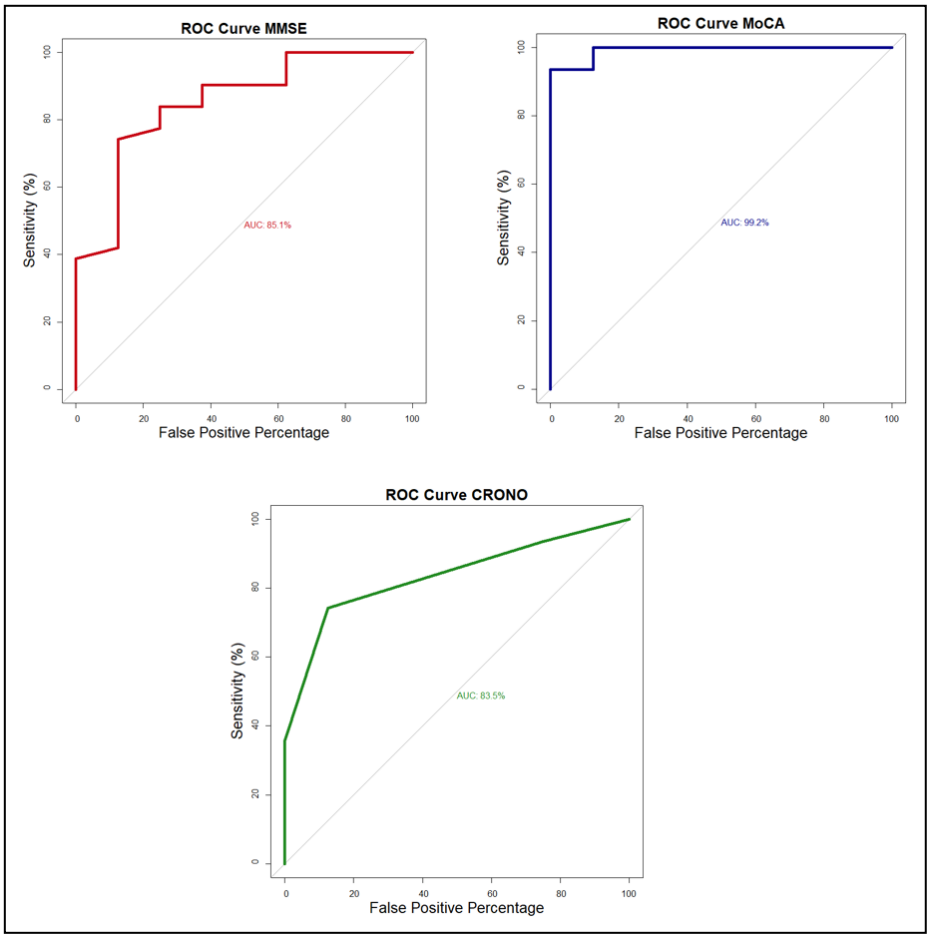


Figure 13 | ROC curves depicting predictive ability with respect to subjects' membership in one of the two MMSE groups, MoCA and CRONO. The area under the curve (AUC) corresponds to the subjects correctly discriminated as impaired, which is 85.1 for MMSE, 99.2 for MoCA and 83.5 for CRONO, respectively.

Notably, using only the MoCA gives the same diagnostic response as the entire battery, except for one subject who is are false negative for the MoCA, as can be seen from the ROC curve of the MoCA in Figure 13, the AUC is 99.2 and thus a correct recognition rate of 99%.

As can be seen from Figure 13, the discriminative capability of CRONO is close to that of the MMSE, while the MoCA's is almost perfect. Significance analysis of the difference in discriminative ability (ROC Curve) of CRONO and MMSE was tested by the Hanley-McNeil formula and found to be non-significant, so MMSE and CRONO have comparable discriminative ability.

Overall, the findings from this sample are encouraging in terms of both UX's judgment and CRONO's capacity to discriminate between people with impairment. In the prior investigation, CRONO's discriminative capacity was 65%, which was insufficient at the conclusion of CRONO validation, however, in the present study, CRONO's predictive ability was 83.5%.

3.6 Discussions and Conclusions

In accordance with Pearson and collaborators (2020), a feasibility study is designed to help prepare the ground for a larger, more definitive research that should either improve the chances of the subsequent study producing valuable evidence or help to avoid wasting resources on large studies that are unlikely to answer the intended research question.

The major goal of this study was to determine whether it was feasible to provide a neuropsychology service in pharmacies that was focused on the evaluation of cognitive functioning. The findings are at least encouraging in terms of the potential for the future large-scale provision of this service. The pharmacies included in the trial proved to be very supportive and active participants and important thanks in this regard should be made to the four pharmacies that participated in the research project Pharmacy Baganza 2, Pharmacy Costa, Pharmacy Ponte Dattaro, and Pharmacy Brandonisio. The population was also intrigued by the service, and waiting lists were established for people to use this cutting-edge service. One of the most important aspects to emphasize is *subject empowerment*, which turned out to be the crux of participation in the study. In fact, most of the subjects who participated in the study manifested a decline in memory skills compared with the past, and it is this reason that led them to request memory assessment. Even individuals who were not cognitively impaired expressed curiosity in learning how to sustain this state of functioning after taking part in the study. Patient empowerment is essential to increasing the likelihood that therapy will be effective in the case of chronic, progressive disorders, such as NCDs. In addition to these qualitative observations resulting from the fieldwork, empirical analyses also revealed the actual potential of this service. The UX evaluation of CRONO was well above expectations; of the 39 participants, only 3 subjects needed help in taking the computerized test, and the USQ results are largely positive. In addition, the prediction accuracy of CRONO, was comparable to that of the MMSE, even with the use of the latest calibration (Foderaro et al., 2022), which

in this sample reaches the threshold necessary for the evaluation hypothesis, in particular, the diagnostic accuracy of CRONO was 83.5%. This result, if confirmed by future studies on a larger sample and, with a higher percentage of impaired people, could lead to the validation of the test. The possibility of testing this experimental protocol on a larger sample could also allow us to analyze the existence of a difference in perceived workload, as measured through the NASA-TLX, in the groups of compromised and non-compromised subjects.

3.7 Limits and prospects

Due to the small sample size, there are several limitations to this study. However, the USQ and NASA-TLX qualitative evaluation of CRONO revealed good usability, and this result is crucial because the prior study revealed numerous challenges using CRONO. Positive outcomes in terms of usability were made possible by the adjustments implemented, especially those involving the deployment of the serious game approach and innovations in the graphical user interface. Future research may compare the findings of this initial feasibility study with those acquired following improvements that are expected in the future. In fact, despite the USQ results, CRONO is actually still quite unripe and requires several upgrading. A future analysis that is possible to go to investigate is whether there are differences between the workload associated with CRONO by impaired versus nonimpaired subjects. Given the large numerical disparity between the two groups, it was not possible to investigate this analysis further, the results of which can be found in Appendix - Section 4.

Because the serious game approach is now just explained in terminology, i.e., in CRONO's task description, rather than being definitely a serious game, it will need to be significantly developed in future studies. An interesting prospect would be to introduce "success screens" after performing tasks correctly, such as those shown in Figure 14.

Figure 14 | Hypothetical "success screens" of the two prospective memory tasks.

The CRONO test subjects may become more engaged and motivated if the serious game method is used more consistently. However, this way of assessing PM is not the only one available. In an interesting study in 2021 Zuber and colleagues assessed PM through a completely different task than the one performed in this study. Specifically, through an actual video game, the Geneva Space Cruiser, they assessed PM finding good agreement with the classical assessment (Zuber et al., 2021). In addition to the important differences in the way PM was assessed, the experimental protocol of this study included a questionnaire on computer proficiency using the Computer Literacy Scale (CLS; Sengpiel & Dittberner, 2008), which could be a significant element to include in future studies. However, the keyboard-use screens added to the CRONO version utilized in this study allowed users with little computer experience to complete the two tasks successfully. The memory assessment service has been a huge success in the population, as was predicted in the results section, with lines forming to access it. This finding is important in terms of expanding the sample's study; moreover, additional pharmacies in the city of Parma have already been formally invited to take part in further research with positive replies. However, the participation of MCI patients, possibly outside of the evaluation carried out by UNIPR's Cognitive Psychology Laboratory, is essential for the validation of CRONO. Finding people who have already been diagnosed with AD and whose diagnoses have been supported by MRI and biomarker surveys may one day make it possible to find correlations between brain activity and biomarkers, and performance on the CRONO test, similar to the findings of Caffarra and colleagues (Caffarra et al., 2016), who

were able to confirm particular brain activities with specific FCSRT measurements (Ding & Chan, 2022).

The “Prose Memory Test” task was one of the things that has the most several problems because many study participants chose to perform better the prospective task, over the OT (correctly answering the question about the passage). This is a severe deviation from the prospective task’s ideal arrangement, which places the OT first and the prospective task second (Brandimonte et al., 1996). However, it might be possible to keep this task and add information of clinical significance by implementing the serious game approach, as previously described, and adding a deferred questionnaire, i.e., a multiple-choice test on the excerpts that are presented in the “Prose Memory” task.

In conclusion, building on what was stated in the first chapter and the section on the goals of this study, is feasible to provide a memory evaluation service in pharmacies as a novel approach to screening for cognitive impairment.

The Italian region of Emilia-Romagna may be the first to try out a novel approach to providing a screening service for mnestic functioning to the entire country. In order to suggest rehabilitation plans that are successful at delaying or interrupting e the progress of the disease. It is obvious that this requires competence and knowledge of memory rehabilitation techniques, a field in which Prof. Pino has extensive experience. Although it is not the focus of this research project, the possibility of slowing or halting the progression of NCDs’ pathologies has received considerable attention in the literature. This feasibility study has raised the prospect of encouraging population screening, first in the city of Parma and then throughout the entire region.

Appendix

Section 1

Figure 1 shows the final playbill used to advertise the service in pharmacies participating in the study. Field observation and intercommunication with pharmacists made me reconsider the first prototype poster (Figure 18) as the terminology "cognitive functioning" was too technical and inadequate to attract people to request more information about the service.

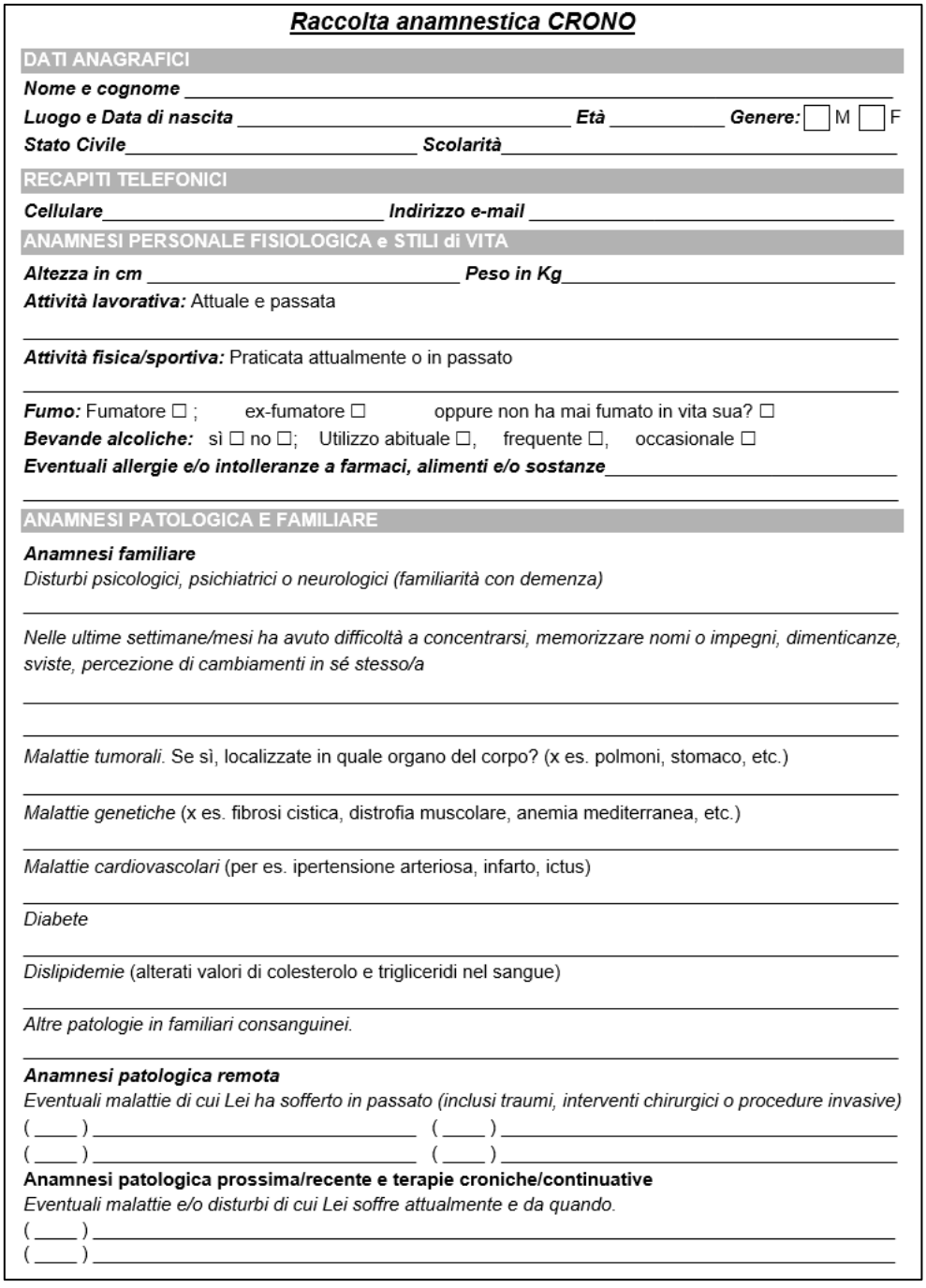
a. First prototype of the playbill

b. Final playbill

Figure 18 | First prototype (a) and final playbill (b) for the pharmacies that participated in the study.

Section 2

Figure 19 shows the amnestic collection format used in the study to collect data on subjects before starting the CRONO Test.



Raccolta anamnestica CRONO

DATI ANAGRAFICI

Nome e cognome _____

Luogo e Data di nascita _____ ***Età*** _____ ***Genere:*** ☐ M ☐ F

Stato Civile_____ ***Scolarità***_____

RECAPITI TELEFONICI

Cellulare_____ ***Indirizzo e-mail*** _____

ANAMNESI PERSONALE FISIOLOGICA e STILI di VITA

Altezza in cm _____ ***Peso in Kg***_____

Attività lavorativa: Attuale e passata

_____

Attività fisica/sportiva: Praticata attualmente o in passato

_____

Fumo: Fumatore ☐ ; ex-fumatore ☐ oppure non ha mai fumato in vita sua? ☐

Bevande alcoliche: sì ☐ no ☐; Utilizzo abituale ☐, frequente ☐, occasionale ☐

Eventuali allergie e/o intolleranze a farmaci, alimenti e/o sostanze_____

_____

ANAMNESI PATOLOGICA E FAMILIARE

Anamnesi familiare

Disturbi psicologici, psichiatrici o neurologici (familiarità con demenza)

_____

Nelle ultime settimane/mesi ha avuto difficoltà a concentrarsi, memorizzare nomi o impegni, dimenticanze, sviste, percezione di cambiamenti in sé stesso/a

_____

_____

Malattie tumorali. Se sì, localizzate in quale organo del corpo? (x es. polmoni, stomaco, etc.)

_____

Malattie genetiche (x es. fibrosi cistica, distrofia muscolare, anemia mediterranea, etc.)

_____

Malattie cardiovascolari (per es. ipertensione arteriosa, infarto, ictus)

_____

Diabete

_____

Dislipidemie (alterati valori di colesterolo e trigliceridi nel sangue)

_____

Altre patologie in familiari consanguinei.

_____

Anamnesi patologica remota

Eventuali malattie di cui Lei ha sofferto in passato (inclusi traumi, interventi chirurgici o procedure invasive)

(____) _____ (____) _____

(____) _____ (____) _____

Anamnesi patologica prossima/recente e terapie croniche/continuative

Eventuali malattie e/o disturbi di cui Lei soffre attualmente e da quando.

(____) _____

(____) _____

Figure 19 | Format for the anamnestic collection.

Section 3

To make sure that the automatic CRONO count was correct, I created this version of "paper CRONO" that I would fill out while the subjects were taking the test on the computer (Fig. 20).

TEST CRONO

Nome e cognome ____

Data ____________________

Memoria di prosa

1. Riconoscimenti corretti 2. Riconoscimenti errati	○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○
1. Riconoscimenti corretti 2. Riconoscimenti errati	○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○
1. Riconoscimenti corretti 2. Riconoscimenti errati	○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○
1. Riconoscimenti corretti 2. Riconoscimenti errati	○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○

Parole bisillabiche

1. Riconoscimenti corretti 2. Riconoscimenti errati	○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○
1. Riconoscimenti corretti 2. Riconoscimenti errati	○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○
1. Riconoscimenti corretti 2. Riconoscimenti errati	○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○
1. Riconoscimenti corretti 2. Riconoscimenti errati	○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○
1. Riconoscimenti corretti 2. Riconoscimenti errati	○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○
1. Riconoscimenti corretti 2. Riconoscimenti errati	○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○

Figure 20 | "Paper CRONO".

Section 4

An interesting future study can be done on the analysis of perceived workload in using CRONO and whether there are differences between compromised and non-compromised subjects. The small sample size, particularly that of the compromised, did not allow this feature to be investigated further.

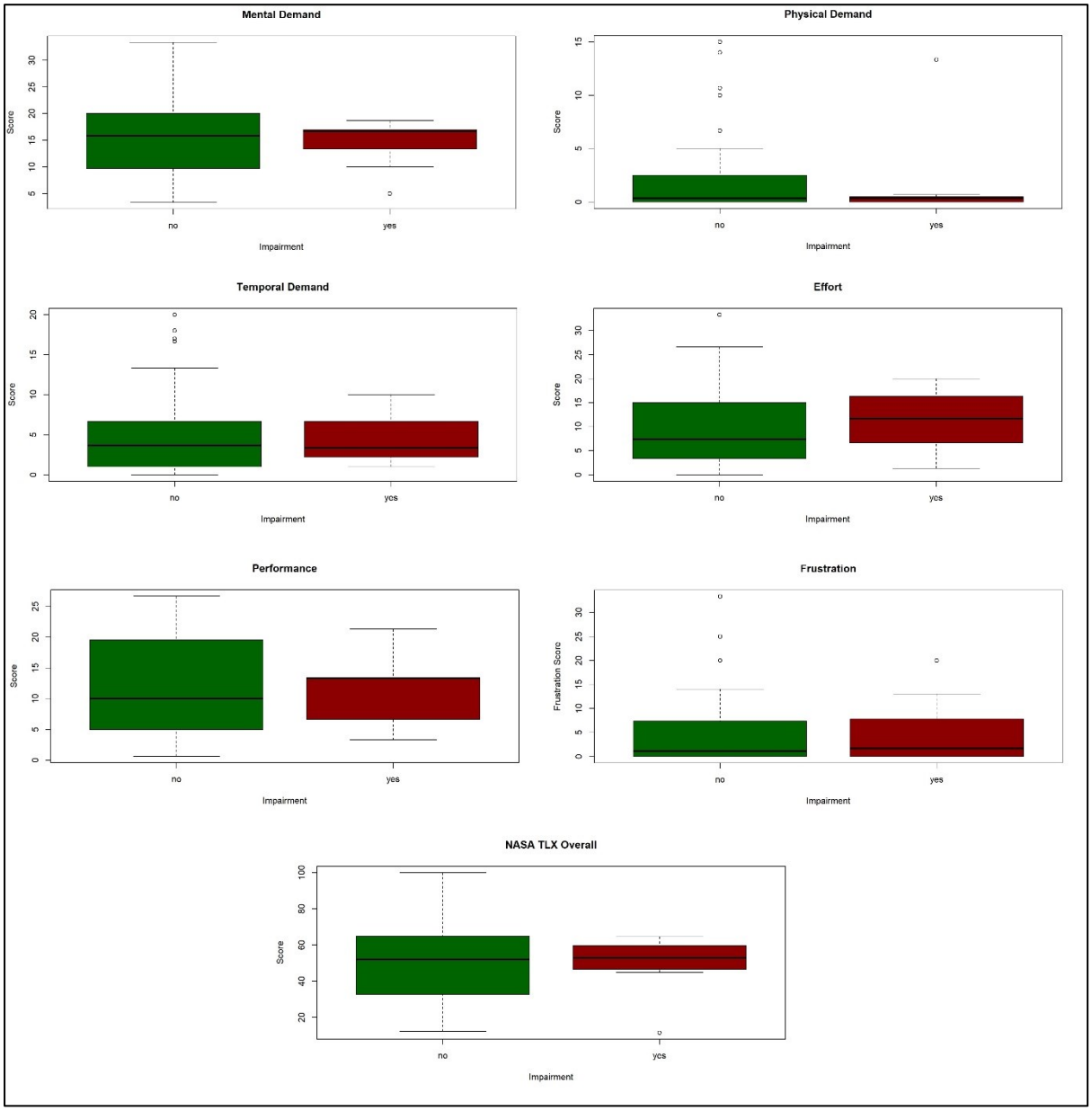


Figure 21 | Boxplots of the six dimensions of NASA-TLX in the two groups.

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