UNIVERSIDAD POLITÉCNICA DE MADRID
ESCUELA TÉCNICA SUPERIOR DE
INGENIEROS DE TELECOMUNICACIÓN

**A METHODOLOGICAL FRAMEWORK FOR
EXPLORING THE APPLICABILITY OF VIRTUAL
REALITY IN COGNITIVE DISABILITIES CARE**

TESIS DOCTORAL

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There is always going to be a reason why you can't do something, your job is to constantly look for the reasons why you can achieve your dreams.

Shannon Miller - 7x Olympic Gymnast medallist

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Abstract

Handling the care needs of people affected by Alzheimer's disease and related dementias (ADRD) represents nowadays a personal, familial and social challenge of enormous proportions, which poses an ever growing human and economic burden on the world's society in general. Information and communication technologies (ICT) have the potential to make a considerable impact to help revert this trend, especially through the use of advanced virtual reality (VR)-based computerized diagnostic and therapeutic cognitive interventions for people living with, or at risk of developing, ADRD. This doctoral thesis aims to facilitate the use of such VR-based interventions. To that end, it makes specific original contributions regarding: the categorization of VR systems particularly designed for ADRD; an analysis and assessment of the current relevance and impact of the 'brain training debate' involving commercial brain training products; an up-to-date critical description of the technical and scientific challenges faced today for the development of effective VR-based cognitive training tools; and finally, this thesis proposes a novel methodological design framework to provide guidance to researchers and developers with the design process of VR-based tools to address the care needs of people with ADRD. The framework is based on our previous critical analysis of the most recent knowledge available about VR cognitive interventions. The framework and its ensuing roadmap take into account, not only universal design principles, standard techniques and methodologies, but also addresses the specific aspects of accessibility and usability that are particular to the use VR-based platforms on patients with ADRD-associated cognitive impairments.

Resumen

El manejo de las necesidades de atención de las personas afectadas por la enfermedad de Alzheimer y demencias relacionadas (EADR) representa hoy en día un desafío personal, familiar y social de enormes proporciones, lo que constituye una creciente carga humana y económica para la sociedad mundial en general. Las tecnologías de la información y la comunicación (TIC) pueden tener un impacto considerable para ayudar a revertir esta tendencia, especialmente a través de la utilización de intervenciones computarizadas de diagnóstico y terapia cognitiva basadas en la realidad virtual (RV), para personas que viven o están en riesgo de desarrollar EADR. Esta tesis doctoral tiene como objetivo facilitar el uso de esas intervenciones basadas en RV. Con este fin, la tesis aporta contribuciones originales específicas relativas a: la categorización de sistemas de RV especialmente diseñados para EADR; un análisis y evaluación de la relevancia e impacto actuales del “debate sobre entrenamiento cerebral” referente a productos comerciales vendidos para ese fin; una descripción crítica actualizada de los desafíos técnicos y científicos que se enfrentan hoy en día al desarrollar herramientas eficaces de entrenamiento cognitivo basadas en RV; y, por último, esta tesis propone un nuevo marco metodológico de diseño para orientar a investigadores y desarrolladores en el proceso de diseño de herramientas basadas en RV para atender las necesidades de las personas con EADR. El marco se basa en nuestro análisis previo de los conocimientos más recientes disponibles sobre intervenciones cognitivas de RV. El marco de referencia y su hoja de ruta toman en cuenta, no sólo principios de diseño universal, técnicas y metodologías estándar, sino también los aspectos específicos de accesibilidad y usabilidad que son particulares para el uso de plataformas basadas en RV por pacientes con trastornos cognitivos asociados a la EADR.

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Acronyms and Abbreviations

ACT:	Accessibility Conformance Testing
AD:	Alzheimer's Disease
ADL:	Activities of Daily Living
ADRD:	Alzheimer's disease or related dementias
aMCI:	Amnesic Mild Cognitive Impairment
AmI:	Ambient Intelligence
APA:	American Psychological Association
AR:	Augmented Reality
B-ODT:	Brief Odor Detection Test
BT:	Brain Training
CAD:	Computer Aided Diagnosis
CCT:	Computerized Cognitive Training
COGA:	Cognitive Accessibility Task Force
CONSORT:	Consolidated Standards of Reporting Trials
CR:	Cognitive Rehabilitation
CT:	Cognitive Training
DBS:	Deep Brain Stimulation
DLB:	Dementia with Lewy Bodies
EC:	Entorhinal cortex
ECG:	Electrocardiogram
EEG:	Electroencephalogram
FDA:	U.S. Food and Drug Administration
fMRI:	functional Magnetic Resonance Imaging
FTC:	Federal Trade Commission
FTD:	Frontotemporal Dementia
FTLD:	Frontotemporal Lobar Degeneration
FUS:	Focused Ultrasound
HCI:	Human-Computer Interfaces
HIS:	Health Information System
HMD:	Head Mounted Displays

IADL:	Instrumental Activities of Daily Living
IATs:	Intelligent Assistive Technologies
ICF:	International Classification of Functioning, Disability and Health
ICF:	International Classification of Functioning, Disability and Health
ICIDH:	International Classification of Impairments, Disabilities, and Handicaps
ICIDH:	International Classification of Impairments, Disabilities, and Handicaps
ICT:	Information and Communications Technologies
ISCTM:	International Society for Clinical Trials and Methods
ISO:	International Organization for Standardization
MCI:	Mild Cognitive Impairment
MMSE:	Mini-Mental State Examination
MoCA:	Montreal Cognitive Assessment
MR:	Mixed Reality
MT:	Mind Training
NA:	Neuropsychological Assessment
NIA:	National Institute of Aging
OT:	Occupational Therapy
PD:	Parkinson's Disease
PET:	Positron Emission Tomography
PSG:	Persona-Scenario-Goal
PSG:	Persona-Scenario-Goal
QoC:	Quality of Care
QoL:	Quality of Life
RCT:	Randomized Controlled Trials
SO:	Strengths-Opportunities
SPECT:	Single Photon Emission Computed Tomography
SS-OIT:	Sniffin' Sticks Odor Identification Test
ST:	Strengths-Threads
SWOT:	Strengths–Weaknesses–Opportunities–Threats

tDCS:	transcranial Direct Current Stimulation
tMS:	transcranial Magnetic Stimulation
UCD:	User Centred Design
VaD:	Vascular Dementia
VEs:	Virtual Environments
VIMS:	Visually Induced Motion Sickness
VPL:	Visual Perceptual Learning
VR:	Virtual Reality
VRAM:	Virtual Radial Arm Maze
VRISE:	Virtual Reality Induced Sickness Symptoms and Effects
W3C:	World Wide Web Consortium
WAI:	Web Accessibility Initiative)
WCAG:	Web Content Accessibility Guidelines
WHO:	World Health Organization
WM:	Working Memory
WO:	Weaknesses-Opportunities
WT:	Weaknesses-Threads

Glossary

AD dementia

The phase of AD where symptoms are sufficiently severe to meet currently accepted dementia and AD diagnostic criteria¹.

Amnestic Mild Cognitive Impairment (aMCI)

A more specified term describing a subtype of mild cognitive impairment, in which there are subjective memory symptoms and objective memory impairment; other cognitive domains and activities of daily living are generally unaffected; affected people do not meet currently accepted dementia or AD diagnostic criteria¹. It has been described as the transitional stage between healthy ageing and dementia. aMCI is characterized by day-to-day memory difficulties and motivational problems².

Alzheimer's disease (AD)

A syndrome with progressive cognitive impairment that becomes severe enough to affect daily activities. AD pathology begins many years before symptoms emerge. The continuously proceeds from asymptomatic stage, to prodromal stage, and finally to the dementia stage³.

From a histopathological point of view, AD may be defined as the appearance of amyloid- β plaques and tau-related neurofibrillary tangles that produce loss of neurons and synapses in the cerebral cortex and in some subcortical regions⁴.

Alzheimer's pathology

Pathology is the gold standard for diagnosis. The hallmarks of disease detected in the brains of patients at autopsy are plaques, mainly comprising β -amyloid deposits outside neurons, and neurofibrillary tangles, which consist mainly of

¹ Dubois, Bruno, et al. "Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS–ADRDA criteria." *The Lancet Neurology* 6.8 (2007): 734-746.

² Savulich, George, Thomas Piercy, Chris Fox, John Suckling, James B. Rowe, John T. O'Brien, and Barbara J. Sahakian. "Cognitive Training Using a Novel Memory Game on an iPad in Patients with Amnestic Mild Cognitive Impairment (aMCI)." *International Journal of Neuropsychopharmacology*, Advance Access Publication, pyx040, 02 July 2017.

³ Frisoni, Giovanni B., et al. "Strategic roadmap for an early diagnosis of Alzheimer's disease based on biomarkers." *The Lancet Neurology* 16.8 (2017): 661-676.

⁴ Tijms, Betty M., et al. "Alzheimer's disease: connecting findings from graph theoretical studies of brain networks." *Neurobiology of aging* 34.8 (2013): 2023-2036.

hyperphosphorylated tau deposits inside neurons and, usually, although not invariably, are co-localised with neuronal and synaptic loss².

Augmented reality (AR)

AR is the real-time use of information in the form of text, graphics, audio and other virtual enhancements integrated with real-world objects. It is this “real world” element that differentiates AR from virtual reality. AR integrates and adds value to the user’s interaction with the real world, versus a simulation⁵.

Biomarker

An objectively measurable substance, characteristic, or other parameter of a biological process that enables assessment of disease risk or prognosis and provides guidance for diagnosis or monitoring of treatment².

Cognition

Mental functioning that is divided into specific domains of mental processes such as attention, memory, and language.

Cognitive control

Neuroscience research has shown that when a person engages into more than one task at once, the brain apparently does not process them in parallel, but switches between different networks that are responsible for processing the tasks.

Cognitive control includes:

- attention,
- focusing mental resources when and where we want them,
- holding information over time,
- and managing multiple goals.

Cognitive stimulation therapy

Is the psychological approach with the strongest evidence for improving cognition. It stems from reality orientation and is usually group-based. It consists of group sessions led by a trained coordinator incorporating social activity, reminiscence, and simple cognitive exercises⁶.

⁵ <http://www.gartner.com/it-glossary/augmented-reality-ar/>

⁶ Livingston, Gill, Andrew Sommerlad, Vasiliki Orgeta, Sergi G. Costafrada, Jonathan Huntley, David Ames, Clive Ballard et al. “Dementia prevention, intervention, and care.” *The Lancet*, In Press, Available online 20 July 2017.

Cognitive training

Involves theoretically driven strategies or exercises targeting specific cognitive domains, usually with an adaptive level of difficulty⁵.

Cognitive rehabilitation

Aims to improve everyday function by helping the patient set individual goals and devising strategies to achieve them. It might be useful for patients with mild-to-moderate AD, for whom individualized goals to improve specific functions could improve functionality and QoL⁵.

Delirium

A temporary disturbance in attention and awareness.

Dementia

Dementia is a complex process involving an interplay between specific molecular pathways affecting cellular functions, leading to loss of synaptic connections, cell death, gliosis¹, inflammation, and disruption of functional networks underlying cognition, personality, behavior and sensorimotor functions, eventually attacking an individual's autonomy. Ageing is the main risk factor for dementia, with more than 90% of dementias presenting after the age of 65 years. Most common dementia syndromes: Alzheimer disease (AD), Frontotemporal dementia, (FTD) Lewy body dementia (LBD), Vascular dementia (VaD), Prion disease / Creutzfeldt–Jakob disease (CJD). AD accounts for approximately 60% of all dementias. For complete description and biomarkers see Ref. Elahi & Miller (2017)⁷.

Major Neurocognitive disorder

A syndrome defined by a severe deficit in cognition and loss of independence in daily living.

Meta-analysis

A meta-analysis (also known as quantitative review) is a statistical tool that combines and quantitatively analyses data results from a systematic integrative review of a number of previously published independent studies on various aspects

⁷ Elahi, Fanny M., and Bruce L. Miller. "A clinicopathological approach to the diagnosis of dementia." *Nature Reviews Neurology* (2017).

of a similar topic, trial or experiment (i.e. a particular treatment or procedure). Its main goal is identifying consistently common outcomes and statistically significant trends across the studies, which would enhance confidence levels and allow achieving a more reliable comprehension of the results (i.e. effectiveness of the treatment or procedure). Meta-studies help overcome the issue of insufficient sample sizes of individual studies because they integrate multiple studies across the same subject area. Meta-analyses can provide valid and dependable conclusions and trends that can influence decisions and suggest new hypotheses to inspire future research and development. Unfortunately, at times they also can produce biased and misleading results. The most probable causes that would result in undependable or even deceptive results are: (1) unbalanced source pools of pertinent studies brought about by widespread journals' bias towards the publication of "positive results" studies, (2) unintentional search engine bias triggered by incomplete or inappropriate sets of search key-words, (3) meta-analysis authors' own selection biases when defining the criteria for inclusion of pertinent studies. For fuller description of meta-analysis and its strengths and limitations see Walker et al. (2008)⁸ and Sánchez-Meca & Marín-Martínez (2010)⁹.

Mild cognitive impairment (MCI)

A syndrome of acquired cognitive impairment without functional limitation that has heterogeneous presentations and underlying pathologies; up to two-thirds of patients with amnesic mild cognitive impairment have underlying Alzheimer's pathology (these individuals are also considered to be at the prodromal Alzheimer's disease stage), 15–25% have neurodegenerative diseases other than Alzheimer's disease (eg, hippocampal sclerosis, frontotemporal degeneration, or Lewy body disease), and the remainder have normal age-related changes¹⁰. MCI is a term used to describe cognitive impairment in one or more cognitive domains

⁸ Walker, Esteban, Adrian V. Hernandez, and Michael W. Kattan. "Meta-analysis: Its strengths and limitations." *Cleveland Clinic Journal of Medicine* 75.6 (2008): 431.

⁹ Sánchez-Meca, Julio, and Fulgencio Marín-Martínez. "Meta-analysis in psychological research." *International Journal of Psychological Research* 3.1 (2010).

¹⁰ Frisoni, Giovanni B., et al. "Strategic roadmap for an early diagnosis of Alzheimer's disease based on biomarkers." *The Lancet Neurology* 16.8 (2017): 661-676.

that is greater than any expected age-related changes, but not of the magnitude to warrant a diagnosis of dementia¹¹.

Mild neurocognitive disorder

A syndrome defined by a decline from a previous level of cognitive functioning that currently does not disrupt daily independence.

Morris Water Maze

The Morris water maze is an experimental setup used to assess spatial navigation skills. In the reality version an animal (typically a laboratory rat) is placed in a water tank and left to freely swim around exploring the space and its walls, with the goal of finding and remembering the location and the fastest route to reach a platform submerged just below the water surface. In the human equivalent of the Morris water maze, the test is carried out not in a physical environment but in a virtual environment instead, using a VR setup.

Neurocognitive disorders (NCDs)

Are defined by a significant decline from a previous level of cognitive functioning. It consists of three syndromes: major NCD, mild NCD, and delirium. Major and mild NCD are diagnosed when an individual shows impairment in at least one of the following cognitive domains: complex attention, executive ability, learning and memory, language, perceptual motor, or social cognition. Delirium is characterized by a temporary disturbance in attention.”¹²

Neuroplasticity

Also known as neural plasticity, brain plasticity and brain malleability, is a wide ranging term used to refer to the hypothesis that says that durable change can occur during a life time at the microscopic and macroscopic scales to the many parts of the brain that are capable of being altered (i.e. are "plastic"). A corollary of this

¹¹ Allan, Charlotte L., et al. "Diagnosing early cognitive decline—When, how and for whom?." *Maturitas* 96 (2017): 103-108.

¹² S.M. Sherman, D.M. Schnyer, "Major and Mild Neurocognitive Disorders," Reference Module in Neuroscience and Biobehavioral Psychology, *Encyclopedia of Mental Health* (Second Edition), 2016, Pages 33–38.

hypothesis is that cognitive abilities, just like physical abilities, can be maintained or enhanced by engaging in brain exercises¹³.

Neuropsychological assessment

A battery of cognitive tests used to assess an individual's level of functioning across a wide range of abilities relative to others of the same age¹⁰.

Preclinical AD

The long asymptomatic period between the first brain lesions and the first appearance of symptoms and which concerns normal individuals that later fulfil AD diagnostic criteria¹⁴.

Prodromal

Pertaining to early symptoms that may mark the onset of a disease¹⁵.

Prodromal Alzheimer's disease

Alzheimer's disease stage after symptoms have begun to manifest but before disability is apparent (ie, during the mild cognitive impairment stage)⁸.

Serious game

Generally refers to a computer-based game with a purpose other than just entertainment, i.e. a cognitive, attention or memory training game.

Spatial ability

Is the ability to process spatial thinking¹⁶.

Spatial thinking

Evidence from neural, cognitive, and linguistic studies indicates that spatial thinking is the use of spatial information for "manipulating, constructing, and navigating the physical world."¹⁷

¹³ Mahncke, Henry W., Amy Bronstone, and Michael M. Merzenich. "Brain plasticity and functional losses in the aged: scientific bases for a novel intervention." *Progress in brain research* 157 (2006): 81-109.

¹⁴ Dubois, Bruno, et al. "Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria." *The Lancet Neurology* 6.8 (2007): 734-746.

¹⁵ <http://medical-dictionary.thefreedictionary.com/prodromal>

¹⁶ Cheng, Yi-Ling. "The Improvement of Spatial Ability and its Relation to Spatial Training." *Visual-spatial Ability in STEM Education*. Springer International Publishing, 2017. 143-172.

¹⁷ Newcombe, Nora S., and Thomas F. Shipley. "Thinking about spatial thinking: New typology, new assessments." *Studying visual and spatial reasoning for design creativity*. Springer, Dordrecht, 2015. 179-192.

Therapeutic applications of VR

Besides brain function research, VR also has been used for therapeutic purposes. According to Bohil VR for therapeutic purposes has been successful in at least three areas of application: psychiatric disorders, pain management, and neurorehabilitation¹⁸.

Virtual reality (VR)

“Is a multimedia interactive experience in which users feel immersed within the computer generated, virtual environment. It is a powerful platform to use for therapy involving exposure to cues, particularly for persons with anxiety disorders. VR exposure (VRE) therapy has been found to be a successful tool for treating many phobias and posttraumatic stress disorder. Advantages of VRE therapy include the therapist having control over the scenarios, the ability to tailor the environments to the client’s needs, and the convenience of being able to provide a range of virtual environments without leaving the therapist’s office.”¹⁹

VR provides a computer-generated 3D environment that surrounds a user and responds to that individual’s actions in a natural way, usually through immersive head-mounted displays and head tracking. Gloves providing hand tracking and haptic (touch sensitive) feedback may be used as well. Room-based systems provide a 3D experience for multiple participants; however, they are more limited in their interaction capabilities²⁰.

General criticisms of Virtual Reality

Early VR equipment was clearly inadequate resulting in initial experiences that were generally unsatisfactory. As a result, public acceptance of VR technology was at first unenthusiastic and its widespread adoption was initially slow. Several criticisms held back implementation of VR in the past. The most common have been those concerning¹⁶:

- Cost
- Requirement for specialist technology skills

¹⁸ Bohil, Corey J., Bradley Alicea, and Frank A. Biocca. "Virtual reality in neuroscience research and therapy." *Nature Reviews. Neuroscience* 12.12 (2011): 752.

¹⁹ Rothbaum, Barbara Olasov, Larry Hodges, and Rob Kooper. "Virtual reality exposure therapy." *Journal of Psychotherapy Practice & Research* (1997).

²⁰ <http://www.gartner.com/it-glossary/vr-virtual-reality/>
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- Bulkiness of equipment
- Cybersickness

Although cost remains an issue, most of the criticisms have faded away today because continued research and industrial progress in VR hardware and software are constantly overcoming most of VR's earlier drawbacks.

Lack of enough developmental guidelines is another problem of VR. The use of more uniform approaches to therapeutic VR system design and deployment would improve VR therapeutic solutions and speed up their adoption.

“As these software and hardware components become ubiquitous, VR may increasingly be viewed as an ordinary part of neuroscience research and therapy.”¹⁶

CHAPTER 1

INTRODUCTION AND PROBLEM STATEMENT

This doctoral thesis entails designing and developing a methodological design framework consisting of methodologies, guidelines and procedures for exploring the use of Virtual Reality (VR)-based technologies to address the care needs of people with Alzheimer's disease or related dementias (ADRD). The term “care” is understood here to involve diagnosis and prognosis, follow-up, mitigation of symptoms, training, improvement of independence and active aging, quality of care (QoC) and quality of life (QoL), all in the context of cognitive health. The intention is to be able to assess applicability and usability issues raised by the interaction of VR techniques and cognitively impaired patients with ADRD.

The central operative principle of the present doctoral thesis is firmly based upon multidisciplinary. It entails embarking in a joint effort among researchers, technical and medical specialists, and caregivers, aimed at an interdisciplinary development of strategies and procedures that will fulfil the patient's specific cognitive care needs, as well as the caregivers' intervention requirements. The approach is multidisciplinary in that it will bring about cross-enrichment among several diverse scientific and technological disciplines such as: Information and Communication Technologies (ICT), e-health technologies, VR technologies, Human-Computer Interfaces (HCI), sensor systems and technologies, cognitive science, sensory perception psycho-physics, neuropsychology, non-invasive health treatment, training strategies, etc.

This chapter contains the general motivation and the problem statement. It presents the current situation of population aging and refers to the impact of cognitive impairments in the older sector of the population. It includes a brief synopsis of the

significance of brain plasticity theories and the possible effect of ICT in the mitigation of cognitive impairments through cognitive training.

1.1. MOTIVATION AND RATIONALE

1.1.1. Population and aging

As life expectancy continues to increase, the number of older people unable to live independently and in need of assistance because of age-related cognitive impairments is rapidly rising worldwide (Cotelli, Manenti, Zanetti, & Miniussi, 2012; Grady & Craik, 2000; Seelye, Schmitter-Edgecombe, Das, & Cook, 2012).

The world's population aged older than 60 years is estimated to grow to about 2 billion by the year 2050 (World Health Organization, 2015). Specifically in Europe, there is a tendency to increase the life expectancy at older ages with a reduction of mortality rates at ages 80 and over. This is mostly due to improved nutrition and living conditions, and to medical care progress and breakthroughs in the health sciences. The reduction of mortality rates together with the effects of current low fertility rates, produce an inversion of the age population pyramid where the size of younger cohorts stabilizes and the older proportion of the total population increases, as shown in Figure 1.1. Such circumstances entail severe social consequences regarding growing family burdens, lesser QoL and well-being, increasing health care demand, long term utilization of care facilities, and so on, all of which generate very significant impacts on health care services demand and costs (Lin et al., 2013; Monteagudo Peña, 2012; Seelye et al., 2012). For example, the worldwide cost of Alzheimer's disease in 2015 was about US\$818 billion, which will translate into an overall cost for the world of about US\$2 trillion by the year 2030 (McDade & Bateman, 2017). At the same time, studies about the social impact of care show that the costs of home care can be considerably lower than those of institutional care

(Bowes, Dawson, & Greasley-adams, 2013; Gaßner & Conrad, 2010). Consequently such type of studies often propose increasing the use ICT application as a potential answer to:

1. Support older people at home for longer periods, avoiding needs of institutional forms of care;
2. Reduce costs of health care services; and to
3. Provide personalized solutions to enhance older people living standards.

Figure 1.1 - Evolution of the Population Pyramid in Europe (Source: <http://populationpyramid.net/world/>)

1.1.2. The impact of Cognitive Impairment in the older population

Memory declines with psychological aging and causes people to experience memory problems (Cotelli et al., 2012; Schmitter-Edgecombe & Woo, 2009). Several clinical conditions include memory impairments among their symptoms caused by a progression from normal aging to other cognitive conditions, such as Mild Cognitive Impairment (MCI) or Dementia (Kirk-Sanchez & McGough, 2014; Kwok et al., 2013). Dementia is a progressive degenerative brain syndrome that involves memory impairment in older adults caused by damage to brain cells and their connections. It affects memory, thinking, behavioural and emotional state, orientation, comprehension, calculation, learning capacity, language, judgment, and the ability to perform everyday activities (Thies & Bleiler, 2011; WHO, 2012).

Memory impairment is one of the main cognitive issues that contribute to the inability to live independently, social isolation and a progressive loss of autonomy (Cotelli et al., 2012; Garcia, Kartolo, & Méthot-curtis, 2012; Grady & Craik, 2000; Schmitter-Edgecombe & Woo, 2009; Seelye et al., 2012). Memory impairment in the early stages of dementia limits memory processes and reduces older people's autonomy when performing complex daily activities. At the same time it undermines emotional control, social behaviour, and motivation (Monteagudo Peña, 2012; Schmitter-Edgecombe & Woo, 2009; WHO, 2012).

Although dementia is not necessarily part of aging per se, it still represents one of the major causes of disability and dependency among older people worldwide. The World Health Organization (WHO) reported that an estimated 35.6 million people lived with dementia in 2010, and the number is expected to almost double every 20 years, to 65.7 million in 2030 and 115.4 million in 2050 (Prince et al., 2013).

Between about 2% and 10% of all dementia cases begin before the age of 65, and this proportion doubles every 5 years after age of 65. It is estimated that about 7

million people were having dementia in Western Europe in 2011, and these numbers are expected to continue to rapidly increase (WHO, 2012). An estimated 5.2 million people had Alzheimer's Disease (AD) in the United States, of which about 200 000 people are younger than 65 years of age (Alzheimer's Association, 2013). Accordingly, the WHO recommended that dementia should be regarded and handled as a major public health issue because of its widespread high incidence (WHO, 2012). It represents one of the major challenges for health and social services in Europe (Monteagudo Peña, 2012).

There is a growing social demand to significantly improve the quantitative and qualitative efficiency of health care and social support services provided to the general population. Pharmacological treatments for AD are limited to symptomatic management of the condition, but lack any efficacy for treatment or for slowing down the progression of the disease. Alternative treatments and strategies to slow age-related decline and reduce disease-related cognitive impairment in older adults are urgently needed (Farina, Rusted, & Tabet, 2014; Kirk-Sanchez & McGough, 2014). There are studies that indicate that cognitively unimpaired older adults can benefit from training programs. This is especially so because of the existence of preserved cognitive abilities and other factors favourable to enhancing cognitive performance (Adam, Linden, Juillerat, & Salmon, 2000). However, very many fundamental questions still remain to be answered in this particular area of neurocognitive science (Musk & Zuckerberg, 2017).

Early detection of AD has been growing in importance in recent years mainly because of the benefits that the possibility of life planning represents from a practical point of view (Lin et al., 2013). Another important reason is the ability to timely apply early interventions that could slow the course and evolution of the disease, or the

arrival of the most advanced symptoms that generate high levels of disability (Schwindt & Black, 2009).

The prevalence of cognitive impairment not categorized as dementia is about 22% among older adults, with around 12% of them later progressing to dementia (Kirk-Sanchez & McGough, 2014). Specifically, the prevalence of MCI, a diagnosis that is often considered an early transition state between healthy cognitive aging and dementia, among older adults is between 3% and 19%, and from 20% to 50% of these individuals have a high risk of developing dementia over a period of 2 to 3 years (Belleville et al., 2006; Morris et al., 2001; Seelye et al., 2012; Thivierge, Simard, Jean, & Grandmaison, 2008). About 10% to 55% of cases with MCI later turn into dementia over a 2- to 6-year period. This means that MCI can act as a predictor of dementia (Farias et al., 2006; Morris et al., 2001; Schmitter-Edgecombe & Woo, 2009; Seelye et al., 2012). Although people with MCI have impairments related to episodic memory and some deficits in attention, language, visuospatial abilities, and executive function abilities, such individuals in general fail to meet standard criteria for dementia. Thus, most research studies are focused on applying cognitive training programmes to individuals in this previous stage of AD, because this phase is considered a crucial period to try to promote brain plasticity and reduce cognitive symptoms (Belleville et al., 2011; Optale et al., 2010).

Projection models show that prevention and early detection, together with the detection of the risk factors involved, are key elements for the reduction of the incidence and future prevalence of AD. It is estimated that delaying AD onset by 1 year could contribute to reduce the total worldwide number of cases in 2050 by 11%. There are also other models that suggest that, even delaying the onset, the total number of cases will probably continue to increase because of the projected population aging, as illustrated in Figure 1.1. On the other hand, the increasing

incidence of related risk factors could be potentially modified through adequate early intervention (Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007; Jagger et al., 2009; Norton, Matthews, Barnes, Yaffe, & Brayne, 2014). Figure 1.2 presents an infographic based on the just mentioned factors, data, statements and analysis, summarizing the impact of AD and MCI among older population.

Figure 1.2 – Dementia and Alzheimer’s disease facts (from various sources mentioned in the text).

1.1.3. Brain Plasticity

Recent studies have demonstrated the ability of the adult brain, and even of a damaged brain, to adapt to environmental stimulus by changing the connections between neurons and learning new behaviours (Esteves Moreira da Costa & Vidal de Carvalho, 2004). This adaptability idea is rooted in the general concepts of lifelong neuroplasticity. From the first year of life to death the brain seems to continuously refine its “organisational mechanisms,” building upon experience, knowledge, and a wide spectrum of skills and abilities (Merzenich, 2004). During this time, the brain is ever changing and refining under behavioural control, continuously adjusting to environmental experiences (Herrera, Chambon, Michel, Paban, & Alescio-Lautier, 2012). It is well known that cognitive enrichment early in life, together with genetic and lifetime environmental factors (e.g. social lifestyle and physical activity), produce an impact in the development and physical structure of the brain and determine cognitive function. But there is also, evidence that indicates that cognitive functioning can be maintained and improved even among elderly people, (Anguera et al., 2013a; Calero-García, Navarro-González, & Muñoz-Manzano, 2007; Herrera et al., 2012). Such changes can occur after continued (over long periods of time) and repeated practice of a skill, leading to the modification of neural structures and functions, as evidenced by the ability of the brain to “compensate for pathological changes associated with aging” (Herrera et al., 2012; Rabipour & Raz, 2012).

The brain has a cognitive reserve ability to more efficiently use brain networks, or use alternative networks, in order to maintain normal cognitive task performance (López et al., 2014). Mechanisms such as non-synaptic neurotransmission, where the communication is performed through the release of neurotransmitters from remote sites, have also been identified as processes used by the brain to reorganize and recover lost cognitive functions (Bach-y-Rita, 2003; Yu et

al., 2009). Many studies have highlighted the importance of brain plasticity and suggested the use of cognitive training because of its potential benefits for restoring cognitive function and for delaying the progression of cognitive decline in neurodegenerative diseases such as Alzheimer's Disease (AD), (Bach-y-Rita, 2003; Calero & Navarro, 2004, 2007; Herrera et al., 2012; Yu et al., 2009).

1.1.4. The role of ICT emerging applications

Information and computer technology (ICT)-based health care applications specifically designed for the elderly patients can considerably contribute to alleviate this presently growing problem. Research, development, and implementation of novel computer-based ICT applications for not yet covered needs in the field of cognitive impairment detection, evaluation, mitigation and training can considerably contribute to address this problem (Vahia & Ressler, 2017). Emerging ICT applications based on VR environments, including such novel means as Augmented Reality (AR) technology, can become important game changers to delay the evolution of cognitive impairment and improve the quality of life, independence, and performance of daily living activities of people with ADRD (Torous, 2017).

There is still insufficient knowledge and experience on the use of advanced ICT such as VR environments for cognitive intervention in the treatment of MCI and patients with early dementia. Increasing and strengthening research activities related to VR platforms offers the possibility of more clearly ascertaining the potential efficacy of this technology as a useful tool for cognitive interventions in ADRD, including cognitive training (CT). A deeper knowledge and experience in this field is needed to allow the application of novel concepts, approaches, and methods to the treatment of dementia (Robert, Leroi, & Manera, 2016). Numerous VR systems for cognitive treatment of ADRD, as well as for assessment and diagnosis, have been

developed in recent years. Most of them have not provided the high level of immersion and interaction that would be desirable for this type of interventions. Rather, most have used conventional graphic workstations to create non-immersive scenarios (Anguera et al., 2013b; Bartolomé, Zapirain, & Zorrilla, 2012; Burdea et al., 2013; Chapoulie & Guerchouche, 2014; Coyle, Traynor, & Solowij, 2015; Lee et al., 2014; Serino, Morganti, Di Stefano, & Riva, 2015; Shamsuddin, Ugail, Lesk, & Walters, 2012; Tarnanas et al., 2013; Tarnanas, Tsolaki, Nef, Müri, & Mosimann, 2014; Tu et al., 2015).

Furthermore, the overall efficacy of VR interventions for CT sometimes has been difficult to establish on the basis of results gathered from assessments and clinical trials, mostly because of the absence of generalizable results from consistently common methodologies across trials and VR systems, as well as because of the generally uncoordinated nature of the different heterogeneous studies. In light of this state of affairs, the development of methodological and technical common procedures is an urgent priority that must be addressed before VR interventions can be confidently offered as effective options to complement traditional treatment practices (Ortiz-Catalan et al., 2015).

The growing trend towards personalized healthcare (Personalized Medicine Coalition, 2014), together with recent advances in VR and 3D technologies, points at the impending necessity of improving existing medical VR applications. Such improvement should start by developing better immersive systems based on innovative and easy-to-use technologies - e.g. novel head mounted displays (HMD), 3D smart screens, and so on - that will also allow transferring the applications in a feasible, affordable, and easy way, into home or nursing home environments. Home-based intervention scenarios have to be considered and further explored by multidisciplinary teams of experts that would develop and design affordable, user-

friendly and motivating VR systems for cognitive intervention (Koenig & Krch, 2012). In this regard, we have already suggested in (Garcia-Betances, Jimenez-Mixco, Arredondo, & Cabrera-Umpierrez, 2014) that future cognitive rehabilitation VR platforms, in addition to their main intended purpose, should also provide timely information and support to assist clinicians and caregivers to help improving the quality of living of ADRD patients and their families. A very useful improvement in that direction would be to include real-time feedback mechanisms to allow specialists' access to information captured during the course of the therapy. Such data would provide valuable up-to-date information about the patient's performance, adherence to treatment, rehabilitation evolution, etc. Additionally, the gathering of the feedback data would generate a systematic and robust knowledge base for analytical purposes.

1.2. PROBLEM STATEMENT

Addressing the care needs of people affected by ADRD-related cognitive disabilities through the use of VR-based technologies, in the general context just described, could considerably benefit from the existence of a methodological frame of reference for exploring the applicability of potential VR-based intervention platforms and applications. The framework, consisting of design methodologies, guidelines and procedures, is intended to function as a valuable guidance tool to better meet the many applicability challenges faced by such systems.

Some of the particularly distinctive reasons for using VR-based cognitive intervention systems, such as the goal of improving ADRD patients', their families', and their caregivers' overall QoC and QoL, or enhancing long-term patient motivating and adherence, pose stern requirements on the design of any such system that are best addressed through systematic methodologies. Additionally, due to the still relatively incipient experience with VR-based intervention applications for cognitive training

and disease evolution follow-up, new designs should also assume the role of test platforms that are able to provide much needed systematic and reliable assessment information, to be used by cognitive impairment specialists, as well as by interdisciplinary teams in future improvements and developments.

The implementation of this type of VR-based cognitive interventions opens up enormous possibilities for innovation beyond the present state of the art in several domains and operational conditions that are taken into consideration in the framework. They are related to important characteristics of prevention, detection, treatment, assessment, and symptom and behavioural effects mitigation of ADRD cognitive impairment. Some of the more relevant aspects are mentioned below:

- The active involvement of specialists, caregivers, and even users in the interdisciplinary process of designing and developing the VR system specifically for cognitive training and assessment, in correspondence to their circumstances, unique needs, and appropriate customized training protocols.
- The availability of advanced, adaptable, and easy-to-use multisensory VR interfaces and interaction techniques, where strategies and procedures for patients' interaction and navigational tasks can be developed, tested, and adapted to individual patient's needs.
- The convergence of diverse behavioural, cognitive, and experimental scientific and technological means and approaches into a multidisciplinary integrated setting.
- The accessibility to a high level of experimental control, allowing the intervention, assessment and subsequent study of diverse brain-stimulation activities within different areas: memory, attention, language, executive functions, and functional activities of daily living, etc.

- The availability of real-time feedback and data collection capacity, to gather performance information during the course of the cognitive training activities, to be used for analysis of patients' evolution, as well as for procedure applicability and effectiveness evaluation and tuning.
- The systematic production of robust facts and statistics to be used for analysing the efficacy of VR-based cognitive interventions, especially CT therapies for ADRD patients, which can become a source of reliable information for further research into this field.

The development of this systematic methodological design framework constitutes a highly desirable endeavour that can assist multidisciplinary research teams and developers of VR-based cognitive intervention applications by providing them with a common design methodological approach. The framework and its ensuing roadmap not only take into account universal design principles, standard techniques, and methodologies, but also addresses specific aspects that are particular to VR-based cognitive intervention applications and their technological platforms. The systematic methodology provided by this framework can also steer the design in the direction of improving the accessibility and enhancing the experience of people with ADRD when confronting new ICT technologies in general, and specifically VR-based cognitive interventions.

DOCUMENT STRUCTURE

The rest of the chapters of this doctoral thesis are organized as follows:

Chapter 2 introduces the conceptual foundations of the core matter of the present doctoral thesis, to offer the reader a succinct vision of the main basic concepts involved in the conduction and accomplishment of this research. The foremost fundamental concepts considered are: Virtual Reality systems; Dementia and Alzheimer's Disease, foundations, causes, diagnosis, symptoms, progression, treatment, and assessment; and Therapeutic interventions for Alzheimer's Disease.

Chapter 3 focuses describing the Research Questions and the principal and specific objectives of the research.

Chapter 4 presents the materials used to complete the research work, and describes the methodological phases followed to accomplish the research objectives.

Chapter 5 offers a comprehensive review and analysis of how the use of VR technology can assist in the assessment of MCI and early-stage AD cognitive impairment and support the mitigation of its symptoms and effects.

Chapter 6 discusses the impact of the ongoing debate about commercial brain training products on the development of cognitive training paradigms in general, and specifically on research and development activities that involve innovative ICT-based neurocognitive training interventions for mild cognitive impairment and related cognitive deficits.

Chapter 7 explains the course of defining a methodological design framework for VR-based cognitive interventions. It describes the proposed framework itself, including its conceptual context, components, structure, and procedural roadmap.

Chapter 8 contains the conclusions and discussions that link the research questions and objectives with the answers and results achieved within this work. It

also presents a concise closing account of the original contributions made by this work to current scientific knowledge. It finally offers recommendations for possible lines of future work.

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CHAPTER 2

CONCEPTUAL FOUNDATIONS

This chapter provides conceptual descriptions of the most important topics that conform the theoretical background of this thesis' core theme. The presented descriptions are as brief as possible, but complete enough when needed to explain or exemplify the more unfamiliar terms and concepts. The explanations of the main subjects are duly complemented by abundant citation of appropriate references.

2.1. VIRTUAL REALITY

The operation of Virtual Reality (VR) technology is based on the use of various components of psychophysical perception, of which the most important is the visual component, possibly aided by other sensory perceptions such as auditory, tactile and kinesthetic sensations. VR's essential characteristic is 3D or stereoscopic vision, which is the binocular perception of two slightly differing views (one from each eye) as a single image, resulting in the perception of depth by the brain. 3D vision is the normal natural vision that humans and most animals have. VR technology recreates stereoscopic vision by synchronously presenting two slightly different views of an image to the left and right eyes through the use of some kind of modern binocular optical and/or electronic viewing device. The use of VR systems allows us to create virtual reality scenarios through graphic simulation. The VR environments can become interactive through the use of controllers, and immersive by way of either a mobile smart phone holder-type VR headset or, better yet, a computer-connected VR Head Mounted Display (HMD), to produce a vivid sense of "being there". Of course, other more advanced emerging 3D visual presentation technological options, from holography to smart glasses, to active intraocular lenses, can and will be considered for future use as they become ready and available.

VR provides the possibility of carrying out user-centred experiments, studies and tests within a customisable real-like or imaginary environment, which can be adjusted to the objectives of the experience according to the characteristics of, and the real-time feedback from, the individual user (Optale et al., 2010; Riva, 1998). The core of VR is the virtual environment (VE). Traditionally VEs have been defined as: *“interactive, virtual image displays enhanced by special processing and by non-visual display modalities... to convince users that they are immersed in a synthetic space”* (Ellis, 1994).

Numerous VR software applications that use VR technology, from virtual immersive scenery tours, to interactive training, to ingenious first person games, have been already introduced into dementia care to assist patients and their families by providing memory aids and educational support (Garcia-Betances, Jimenez-Mixco, Arredondo, & Cabrera-Umpierrez, 2014).

2.1.1. Presence and immersion

Slater et al. (Slater, Lotto, Arnold, & Sanchez-Vives, 2009) describes the concept of the “level of immersion” offered by a VR system by referring to the “fidelity” to real- world sensory experience offered by the system’s displays and tracking in all sensory modalities. Some features of VR systems are most significant when characterizing the immersion level (Baus & Bouchard, 2014; Ma & Zheng, 2011; Slater et al., 2009). They may be reduced to four main types:

- a. number of stimulated senses;
- b. quantity and level of interactions;
- c. synthetic stimuli fidelity, and
- d. system’s ability to isolate the user from external stimuli.

Based on the above considerations, three basic levels of system immersion can be defined: non-immersive, semi-immersive, and fully-immersive. In a non-immersive system, the patient interacts with the VE using conventional graphic workstations (e.g. PC monitor, keyboard, and mouse) (Costello, 1997; Ma & Zheng, 2011). Virtual tasks played as serious videogames even when displayed on 2D screens are considered for the purpose of this review as “non-immersive” VR, irrespective of the perspective used to look at the scene, whether be it an overhead view or a first-person view, commonly referred to as survey and route perspectives (Marková, Laczó, Andel, Hort, & Vlček, 2015). Other more dedicated devices, such as joysticks or gamepads may substitute the mouse. A semi-immersive VR system typically consists of more sophisticated graphics, with larger flat surface displays to present the visual VE (Ma & Zheng, 2011). A fully-immersive VE might consist of huge surrounding projection surfaces, or preferably of 3D displays, such as HMDs, that virtually place the patient inside the VE for the highest level of immersion (Baus & Bouchard, 2014; Costello, 1997).

Immersion plays a crucial role on the subjective sense of “presence.” The term “presence” in the context of VR refers to the experience of the feeling of “being there,” that is, how well the VE truly represents a real-world situation, instead of being a simple video viewing experience. “Presence” is strongly related to immersion, since increasing the immersion level induces a higher intensity of the subjective sense of “presence” experienced by the patient. The sense of “presence” intensity experienced by the patient while performing the required tasks, substantially affects the ensuing behavioural responses. This fact was confirmed in a detailed comparative study of the effect of fully-immersive 3D stereoscopic VEs versus less immersive 2D presentations on brain functions and the subsequent behavioural outcomes of VR experiments (Slobounov, Ray, Johnson, Slobounov, & Newell, 2015).

Immersive VR experiences can be further complemented by the addition of augmented reality (AR) and mixed reality (MR) capabilities. AR experiences add a synthetic tier onto an existing view of the world. Still the paradigm of immersive 3D content in VR continues to enlarge its bounds. In addition to 3D vision and sound, hands and body spatial tracking abilities, advanced haptics controllers, other sensory attributes like touch and smell, and even emotional state recognition, are constantly being integrated into yet fuller immersive VR experiences. Such highly enhanced sensory perception immersive VR platforms will allow to place the user into an ever wider range of synthetic interactive environments, ranging from highly realistic similes of the natural world to entirely fictional imaginary worlds.

2.1.2. Motion and simulation sickness

Health and safety implications of the use of VR applications must be given very thoughtful consideration (Nichols & Patel, 2002), especially when intended for cognitively impaired patients. Cyber-sickness, a visually induced motion sickness (VIMS) reaction (Keshavarz, Riecke, Hettinger, & Campos, 2015) that could arise during or after immersion in a VE, should be a matter of serious concern when designing and using such applications (Bohil, Alicea, & Biocca, 2011). The possible occurrence and intensity of VR-induced motion sickness symptoms and other effects (VRISE) is immersion level dependent. Experiments have been conducted to comparatively evaluate VRISE in four VR immersion conditions: Head Mounted Displays (HMD), PC display, projection screen, and reality-theatre. In general, higher prevalence of VRISE was found the more immersive the environment is, although high subject variability was also found (Sharples, Cobb, Moody, & Wilson, 2008).

2.2. DEMENTIA

Dementia is a heterogeneous class of diseases that can be characterized by a decline of cognitive domains due to damage or death of nerve cells (neurons) in different parts of the brain. The symptoms include progressive decline in cognition, and physical and global functioning that consequently affect the ability to perform activities of daily living (ADL) (Alzheimer's Association, 2017a; Flynn et al., 2003; Lin et al., 2013). According to the National Institute on Aging (NIA) and the Alzheimer's Association 2011 guidelines (McKhann et al., 2011) Dementia is diagnosed when there are cognitive or behavioural (neuropsychiatric) symptoms that match the following five principles:

1. interfere with the ability to function at work or at usual activities;
2. represents a decline from previous levels of functioning and performing;
3. cannot be explained by delirium or major psychiatric disorders;
4. cognitive impairment is detected and diagnosed through a combination of patient's history and objective cognitive assessment; and
5. cognitive or behavioural impairment involving a minimum two of the following domains: acquiring and remembering new information, reasoning and handling of complex tasks, visuospatial abilities, language functions, and changes in personality or behaviour.

Dementia can be classified on the basis of the cause, or set of causes, that leads to the development of the symptoms or condition (McKhann et al., 2011).

The most common cause of Dementia nowadays is Alzheimer's Disease (AD), which accounts for an estimated 60% to 80% of cases (Alzheimer's Association, 2017a); followed by Vascular Dementia (VaD), with about 10% of dementia cases; Dementia with Lewy bodies (DLB); and Frontotemporal Dementia (FTD) (Lin et al., 2013). The following list shows the main categories of dementia as described by their

associated characteristics (Alzheimer's Association, 2016, 2017a; Khan, Kalaria, Corbett, & Ballard, 2016; Walker, Possin, Boeve, & Aarsland, 2015).

- *Alzheimer's disease (AD)*: is caused by a progressive accumulation of the protein fragment beta-amyloid outside neurons and twisted strands of the protein tau inside neurons. Early symptoms include memory difficulties, apathy and depression. Later symptoms include impaired communication, disorientation, behavioural changes and, in the last stages, difficulty speaking, swallowing and walking.
- *Vascular dementia (VaD)*: is known as a post-stroke dementia due to impaired blood flow and blood vessel blockage that leads to depriving brain cells of vital oxygen and nutrients. Early symptoms include impaired judgment or ability to make decisions, planning and memory. Regarding physical symptoms it could include difficulties with motor function, slow gait and poor balance.
- *Dementia with Lewy bodies (DLB)*: is caused by an abnormal aggregation of the protein alpha-synuclein in neurons within the brain cortex called Lewy bodies. Some of the early symptoms are the same as AD, but also include symptoms of sleep disturbances, well-formed visual hallucinations, slowness, and gait imbalance. People with Parkinson's disease have also Lewy bodies, but in contrast the onset of the disease is identified by motor impairments and not by cognitive impairment like in DLB.
- *Mixed dementia*: is defined by the simultaneous combination of more than one cause of dementia, most commonly AD with VaD, followed by AD with DLB, and AD, with VaD and DLB. Symptoms depend on the brain regions affected and the cause of dementia implied.

- *Frontotemporal lobar degeneration (FTLD)*: is caused by damage on nerve cells in the frontal lobe and temporal lobes of the brain. The upper layers of the cortex also become soft and spongy together with abnormal protein inclusions. Early symptoms include personality and behaviour changes and/or difficulties with language.
- *Parkinson's disease (PD)*: is caused by an aggregation of alpha-synuclein in the substantia nigra of the brain that causes a degeneration of the neurones that produce dopamine. Symptoms include difficulties with movement. 80% of people with PD progress to dementia because of the accumulation of Lewis bodies or beta-amyloid clumps and tau tangles.
- *Creutzfeld-Jakob disease*: is caused by a destruction of brain cells that may be hereditary, unknown cause / sporadic, or due to the Misfolded prion protein. Symptoms include decline in thinking and reasoning, involuntary muscular movements, confusion, difficulties walking and mood changes.

2.3. ALZHEIMER'S DISEASE

German neuropathologist Alois Alzheimer presented the first formal description of the disease, which was to be later named after him, on November of 1906, at the Southwest German Psychiatrists Society's 37th meeting, in Tübingen, Germany (Goedert & Spillantini, 2006). The following year Alois Alzheimer's lecture describing the clinical and neuropathological characteristics of the disease was published in the German General Journal of Psychiatry and Psychological Forensic Medicine (Alzheimer, 1907).

Alzheimer's Disease (AD) can be succinctly described as a devastating neurodegenerative disease that impairs memory and cognitive faculties. It is frequently accompanied by disorientation, mood changes, odd behaviour, paranoia,

agitation, delusions, and eventually delirium. It progressively deprives its sufferers of their ability to remember, reason, spatially orientate and make other informed judgments. The American Alzheimer's Association, defines AD as “*a neurodegenerative dementia that causes problems with memory, thinking, and behaviour. Symptoms usually develop slowly and get worse over time, becoming severe enough to interfere with daily tasks and functional survival*” (Fargo, 2014). Currently AD is widely considered to be a catastrophic disease. In the words of Jack C. de la Torre, it is “the most common and irreversible destroyer of the human brain. It conveys not only an unfaltering death sentence but an extended period of suffering, humiliation, and confusion before dying” (de la Torre, 2016).

AD is the most prevalent age-associated neurodegenerative disorder, and the most frequent cause of dementia among older adults (National Institute of Health, 2016). In 2015 there were from 28 to 38 million people affected worldwide (Prince et al., 2015). Since the world population as a whole is aging due to sustained life expectancy growth in most countries, AD is anticipated to reach pandemic proportions around 2050, causing enormous human suffering and ruinous economic burdens. It is expected that the worldwide number of AD patients will more than double during the next 35 years. Caring for people living with AD will entail very high physical, emotional, and financial costs at the personal, familial and societal levels (National Institute of Health, 2016). Moreover, societies in low- and middle-income countries will be affected the most (Dolgin, 2016). According to Roberson and Mucke, the imminent worldwide rise in the number of AD cases over the next decades “*makes the development of better treatments a matter of utmost importance and urgency*” (Roberson & Mucke, 2006).

2.3.1. AD Pathogenesis

AD is a complex, heterogeneous and multifactorial disease that has many possible different causes which are involved in, or contribute to, its pathogenesis. A way of defining AD from a histopathological point of view is as the occurrence of amyloid- β plaques and tau-related neurofibrillary tangles that bring about loss of neurons and synapses in the cerebral cortex and in some subcortical regions (Tijms et al., 2013). Two major molecular pathologies of the brain that are known to play vital roles in AD progression. They are: (a) cerebral β -amyloidosis: the accumulation of Amyloid- β ($A\beta$), a peptide protein fragment that can misfold, into insoluble sticky aggregates (plaques) around brain neurons; and (b) the formation of tau protein intracellular neurofibrillary tangles, neuritic plaques, and neuropil threads (Brier et al., 2016). Neuronal loss results in serious atrophy of the affected regions, including degeneration in the temporal and parietal lobe and parts of the frontal cortex and cingulate gyrus (Wenk, 2003).

Tau and $A\beta$ topographies have been correlated to low scores of neuropsychological performance in the areas of episodic, semantic, and working memory, and visuospatial processing, as well as in overall (global) performance (Brier et al., 2016). It appears that, for the purpose of tracking the early symptoms of AD from its non-symptomatic preclinical stages to its symptomatic mild stage, tau deposition in the temporal lobe is a better predictor of cognitive decline than $A\beta$ deposition in any region of the brain.

In addition to the above mentioned hypotheses, there is a large corpus of accumulated solid evidence that seems to indicate that the progression of AD actually consists of a rather complex pathophysiology, which involves damage to neural circuits. Structural brain networks, whose connections correspond to inter-regional axonal pathways, are directly affected by AD because of connectivity disruption in

several areas of the brain, including the cingulate cortices and the hippocampus (Rose et al., 2000; Zhou et al., 2008).

Research work to better understand the factors, mechanisms and relationships implicated in AD's onset and deterioration processes continue to be vigorously pursued, in the attempt to develop therapeutic strategies that may one day help to lessen AD's dreadful burdens (Canter, Penney, & Tsai, 2016). However, the magnitude of present efforts might not be enough. According to Richard Hodes, Director of the USA NIH's National Institute on Aging, stronger research efforts need to be given a boost “...to find the keys to solving the riddle of Alzheimer's disease” (Hodes, 2016).

2.3.2. AD stages

According to the USA National Institute on Aging/Alzheimer's Association Diagnostic Guidelines for Alzheimer's disease, three stages of AD may be distinguished (Jack et al., 2011; Sperling et al., 2011):

- Preclinical – An initial phase in which the brain experiences changes, including amyloid build-up and other early neuron changes. It may occur years before significant memory, cognitive or behavioural clinical symptoms are detectable. The risk for progression from this phase to Alzheimer's dementia is still unknown. Nowadays reference to this phase is mostly used only within research and academic settings.
- Mild Cognitive Impairment (MCI) – Is a brain syndrome characterized by mild symptoms of memory problems and impairment to perform memory tasks, enough to be noticed and measured on mental status tests, but not severe enough to compromise a person's independence or disrupt day-to-day life activities. Progression from MCI to Alzheimer's dementia may or may not

happen, but in some research settings it is defined as a transitional state between cognitive healthy aging and dementia.

- *Alzheimer's Dementia* –This is the stage where other aspects, beyond memory loss, of cognitive and behaviour decline make significant progression. Aspects such as word-finding ability, vision and spatial orientation, and reasoning or judgment, become increasingly impaired thereby reducing the patient's ability to independently perform everyday life activities. Current scientific and clinical-based guidelines and pathways for diagnosis and treatment of AD are generally associated to this final stage of the disease.

2.3.3. AD early signs and symptoms

There are differences between common age-related cognitive changes and the cognitive changes produced by the presence of AD and AD-related diseases (ADRD). In a recent report named “Alzheimer's Disease Facts & Futures”, the Alzheimer's Association provides a list of signs related to AD that can be used to determine the presence of the disease as compared to other dementias (Alzheimer's Association, 2017a). The signs include: memory loss that disrupts daily life, planning or solving problems (e.g. work with numbers, follow a recipe, etc.), troubles completing familiar tasks (e.g. driving to familiar locations, complete home daily tasks, etc.), confusion with time and place, troubles understanding visual images and special relationships (e.g. colour contrast, distances, etc.), writing and speaking problems, social or work insolation, changes in mood and personality (e.g. depressed, confused, etc.).

2.4. DETECTION, DIAGNOSIS AND ASSESSMENT

The present availability of adequate AD and ADRD detection, diagnostic and assessment tools and resources is notably unsatisfactory. This situation poses unique

challenges to address the increasingly urgent need for providing proper mental health-care for the elderly in today's world's aging population.

Conventional clinical diagnosis of AD today remains essentially based on detection of clinical symptoms. Such exclusively clinical symptomatic assessment procedures have fundamental and practical limitations. Therefore, there is a current tendency towards the development of other diagnostic criteria based on the pathological changes associated with several potential diagnostic biomarkers that are directly related to AD (Frisoni et al., 2017; Isaac, Vamvakas, & Isaac, 2017; Tong et al., 2017).

There has been remarkable progress lately in the development of biomarkers for early detection, diagnosis and prognosis (the forecast of likely progression) of cognitive degenerative diseases such as AD, ADRD and other cognitive impairments. Biomarkers, in the areas of genomics, epigenetic testing, proteomic analysis, magnetic resonance imaging and positron emission tomography, etc., are the most valuable tools available today for accurate clinical assessment (Frisoni et al., 2017). However, these biomarker-based techniques are presently too complex, expensive, and time consuming to be useful as routine instruments for generalised early detection screening of AD and ADRD.

2.4.1. Early detection screening and diagnosis

Current evidence indicates that structural and biological changes start to occur during a preclinical phase of AD that starts tens of years before significant manifestation of clinical symptoms. There are currently several research undertakings that are particularly focused on early diagnosis of AD (Alzheimer's Association, 2017a; Dubois, Padovani, Scheltens, Rossi, & Dell'Agnello, 2016; Ren et al., 2017). Special emphasis is being placed on this important issue because of the growing need

to provide treatment during the early phases of the disease, known as the MCI or preclinical stage. Therefore, early detection seems to be the most effective approach to slow or mitigate the progression of the disease, by delaying cognitive deterioration, preserving brain cognitive health over a longer period of time, and by improving the QoL of people affected by the disease. In that context, several methodologies have been proposed in the search for early diagnosis procedures to detect AD-related initial cognitive decline signs and symptoms.

The current most frequently used option for early detection screening of AD is the use of conventional neuropsychological paper-and-pencil cognitive testing. Although it also requires to be administered and interpreted by specialized personnel, it is nevertheless more affordable and less complex than biomarker-based diagnosis. Fortunately, paper-and-pencil cognitive testing can be adapted to be administered through ICT platforms in the form of computerized testing applications (Robbins & Sahakian, 2002). Such computerized versions of conventional neuropsychological tests represent an alternative that is a significant improvement over paper-and-pencil tests, because computerized tests allow more reliable, flexible, and efficient evaluations, their results can be consistently interpreted without a specialist, and they also can gather considerably more data.

There are also several quick and easy to administer brief cognitive tests that have been successfully used for some time to screen for MCI and ADRD in primary care settings. These handy brief cognitive tests also can be adapted for computerized administration. Examples of such brief tests are the Mini Mental State Examination, (Folstein, Folstein, & McHugh, 1975) and the Montreal Cognitive Assessment (Nasreddine et al., 2005), to name only two of the more representative. It has already been proven that digital versions of these tests can provide increased diagnostic

accuracy over their corresponding conventional counterparts (Müller, Preische, Heymann, Elbing, & Laske, 2017).

Several computerized tools and platforms that support different evaluation strategies for detecting early stages of dementia are currently being developed. Feasibility and validity studies are also being conducted about a number of digital platform-based applications for cognitive testing of people at risk of dementia. Smartphone-based apps are being considered for large-scale data-collection in population cognitive studies (Jongstra et al., 2017). Although the potential of computerized testing of a person's cognitive health is currently still being fully assessed, there seems to be no doubt that cognitive computerized testing holds great promise. One very recent example of such type of tools is the computerized cognitive testing tool “Cognigram”²¹, which has entered the cognitive assessment sector of the US healthcare market, after having received approval as a class II medical device from the U.S. Food and Drug Administration (FDA).

Notwithstanding the available evidence, various experts still believe today that computerized cognition assessment probably will never become good enough to be able to produce definitive diagnosis on its own (Solis, 2017). Whether that ominous prediction will end up being true or not, only time will tell for sure. However, there are good reasons to be optimistic. The belief itself rests upon knowledge of today's available computerized cognitive assessment tools, which are based mostly on straightforward adaptations of conventional paper-and-pencil cognitive tests. We hold the view that it is very probable that ever evolving testing strategies and innovative cognitive assessment protocols, together with emerging and future ICT-based

²¹ <https://cogstate.com/>

advanced platforms and tools will soon change this limited view about the prospects of computerized assessment of human cognitive condition.

It is interesting to notice that some existing standard neuropsychological tests, as well as other types of cognitive exercises, such as maze-type challenges, lend themselves better than others for VR platform implementation. It is also worth pointing out that different types of visual, audio, haptic and even olfactory sensorial perception dysfunction, not used to date, may soon start being used as diagnostic or assessment indicators of MCI and AD-associated impairment within VR-based platform cognitive interventions. It is plainly clear that modern VR/AR technologies are ideally suited for computerized implementation of such innovative sensorial perception testing for cognitive assessment.

2.4.2. Improved diagnosis

Integrating a combination of several disease indicators, i.e. VR-based cognitive testing together with functional imaging and biomarker analysis, into a single assessment protocol, can significantly improve the accuracy and reliability of diagnostic and prognostic procedures. A very promising methodology for precise cognitive impairment diagnostic and status assessment purposes is the concurrent combination of the VR intervention with real-time fMRI (Mueller et al., 2012). This mixture of advanced VEs and imaging tools and devices, although a technological challenge, provides the crucial ability to locate functional brain activity related to several cognitive mechanisms such as attention, semantic memory, topographical navigation, and spatial and episodic memory.

A partial report from the still underway four-year study “Imaging Dementia-Evidence for Amyloid Scanning” (IDEAS)²² was presented at the recent Alzheimer's

²² Evidence for Amyloid Scanning (IDEAS) Study: A Coverage With Evidence Development Longitudinal Cohort Study, National Institute on Aging, U.S. Department of Health and Human

Association International Conference (AAIC 2017), held from 16 to 20 July, 2017, in London, England. The IDEAS study is testing over 18,000 MCI and AD patients with previously verified cognitive impairment through objective conventional symptomatic clinical diagnosis by dementia specialists. The preliminary results from the 4,000 patients already tested so far are astonishing. As was reported at the AAIC 2017 conference, PET amyloid imaging scans of the participants' brains showed that only 54.3% of the MCI patients and 70.5% of the AD patients' brains contained amyloid plaques, which is a core feature of AD. That could well indicate that, according to current amyloid hypotheses, many of those individuals may not really have had the disease at all. Therefore, it is almost certain that they have been erroneously treated and/or inappropriately medicated (Bahrapour, 2017). This remarkable recent revelation serves to highlight once more the urgent need for developing better and more accurate methods to assess AD, and especially for the early diagnosis of its prodromal stage MCI.

2.4.3. Other novel diagnostic procedures

There are some emergent non-conventional procedures that could eventually become particularly useful for MCI and AD detection and diagnosis. Although they are based on non-invasive tests, they are best categorised within the realm of biomarker diagnostic tools. As in the case of those already mentioned more commonly used biomarkers, such as cerebrospinal fluid analysis and brain structural and functional imaging, these novel assessment instruments are also based on the examination of some pathological change known to be associated with the disease or its progression such as, for instance, sensorial dysfunction. To illustrate this kind of emerging diagnostic tools for AD and ADRD, we will describe below in some detail

Services. <https://www.nia.nih.gov/alzheimers/clinical-trials/imaging-dementia-evidence-amyloid-scanning-ideas-study> - <http://www.ideas-study.org/>

two representative promising examples that are potentially amendable to VR implementation.

2.4.3.1. Olfactory dysfunction testing

One non-conventional procedure that seems to be particularly promising for MCI and AD detection and diagnosis is olfactory testing. The mounting evidence that links a deteriorating sense of smell and the occurrence of AD (Doty, 1991; Roberts et al., 2016) has induced neurologists in some dementia clinics to begin administering odour identification tests for screening of elderly patients for early signs of MCI and AD (Djordjevic, Jones-Gotman, De Sousa, & Chertkow, 2008; Gros et al., 2017).

Smell tests, such as the Sniffin' Sticks Odor Identification Test (SS-OIT) (Kobal et al., 1996, 2000), are being used to complement cognitive assessment in identifying people who are at high risk of AD years before the onset of dementia (University of Pennsylvania School of Medicine, 2016). Also, recently, the Brief Odor Detection Test (B-ODT) was proposed as a promising instrument for early diagnosis of cognitive decline (Savvoulidou et al., 2017). A recent study confirms that administering the SS-OIT as a complement to Montreal Cognitive Assessment (MoCA) test (Nasreddine et al., 2005), or an eight question short form version of MoCA (Roalf et al., 2016), significantly enhances the diagnostic accuracy for detecting MCI and AD (Quarmley et al., 2016). In addition to odour identification tests, other types of olfactory deficit tests, such as odour detection threshold and odour recognition memory in MCI (Quarmley et al., 2017), are useful tools for MCI and AD early detection.

Olfactory dysfunction can be used as an indicative sign of some neurological disorders such as MCI, AD and perhaps of other neurodegenerative diseases (Dhillal Albers et al., 2016; Doty, 2017; Masurkar & Devanand, 2014; Ryo et al., 2017). The

idea is that symptoms of olfactory decline, impairment and dysfunction are related to recall ability. Although the precise nature of AD-associated olfactory decline is not yet fully understood, it has been recently demonstrated that it has a heterogeneous nature, meaning that the impairment does not affect equally the detection of all types of odorants. Therefore, by assessing the relative difficulty or inability to identify specific odours, olfactory dysfunction can be used as a discriminatory precise indicator suitable for testing AD presence or susceptibility (Umeda-Kameyama et al., 2017).

The ability to identify particular odours can be measured through various existing olfactory tests. Therefore, olfactory testing seems to be a good candidate for becoming a useful non-invasive tool to detect early memory decline pathology and perhaps even to predict progression from amnesic MCI to AD. However, conventional olfactory testing usually entails arduous and cumbersome tasks that typically involve using an olfactometer in a clinical setting. However, advanced ICT tools, VR technology in particular, could again offer the perfect environment to support and facilitate the administration of olfactory testing for MCI and AD detection and evolution assessment.

But, just as visual, auditory and, to a lesser extent, tactile senses have been common resources of VR environments from the technology's start, the sense of smell has been customarily ignored by VR. That was so until recently. Today it is already possible and practical to embed olfactory sensations as an integral part of a VR experience. Nowadays odorant delivery systems for VR and AR environments, to increase the user's sense of presence, are already commercially available from various sources²³. Therefore, there is no major technical impediment now that prevents

²³ <http://www.olorama.com/en/virtual-and-augmented-reality-with-smells/>

including olfactory testing into a VR-based MCI and AD diagnostic or assessment protocol.

Since it is already known that olfactory testing has a proven potential as a useful tool for AD diagnosis, and considering that it is now technically possible to include odorant delivery within a VR environment, it is to be expected that we will soon see innovative experimental VR-based intervention platforms and applications being developed for AD detection and assessment that will incorporate, as the central diagnostic tool, odorant delivery systems adapted for olfactory dysfunction testing.

Synchronizing smells with the rest of the tasks and situations in a combined VR experience will undoubtedly enhance the lively immersive character of the environment. But more importantly, the introduction of olfactory testing per se will add a very significant diagnostic dimension to add to the assortment of other tests that can be made available in future enhanced VR diagnostic interventions.

2.4.3.2. *Saccadic eye movement testing*

Saccadic eye movement, the normal succession of discontinuous individual eye movements in response to stimuli, is another potential source of information that can be used for cognitive assessment. Saccadic impairment is known to be an oculomotor dysfunction that occurs in AD, and thus, it can be used as an early indicator for quickly detecting AD-associated cognitive impairment.

Recent work has demonstrated its worth as an indicator by applying a quick number-naming test, the King-Devick (K-D) test, to measure saccadic performance dependent visual tracking and eye movement to assist in early detection of MCI and AD dementia (Galetta et al., 2017). Results from initial trials indicate that this test works as a simple and effective screening tool for general discrimination between healthy older adults and those with cognitive impairment. The results show that K-D

test type of assessments can be accurate enough to discriminate between control and MCI and AD affected individuals (Galetta et al., 2017).

Based on the preliminary evidence of the potential utility of Saccadic eye movement dysfunction testing, and considering that it is reasonable to expect that the administration of this type of test could be eased and perfected by its implementation within a VR environment, we believe that this innovative kind of testing is a potential attractive option to conform yet another VR-based cognitive evaluation tool for AD and ADRD.

2.4.4. ICT-based prognosis

The human brain exhibits selective vulnerability when faced with environmental or pathological aggression. That means that different regions of the brain are more or less susceptible to abnormal function as a consequence. In the particular case of AD, disease onset and progression preferentially affect certain brain regions such as the entorhinal cortex (EC) — a brain region involved in memory and navigation, the hippocampus — responsible for memory and learning, and the prefrontal cortex — that covers the front part of the frontal lobe where executive functions are carried out. Conversely, other areas, such as the cerebellum, are not known to be affected by AD. What exactly causes this observed selective affection of the brain by AD is a complex issue not yet well understood.

The EC has been shown to be implicated in the early stages of AD histopathology. The EC is a region of the brain located in the medial temporal lobe, used in memory and navigation that functions as the interface between the hippocampus and the neocortex. The EC-hippocampus system plays an important role in declarative (autobiographical / episodic / semantic) memories and in particular spatial memories including memory formation, memory consolidation, and memory

optimization in sleep. The EC contains a network of navigational brain cells known as *grid cells*, which are involved in spatial navigation. The neurons that make up this grid are arranged in a triangular lattice in the EC.

The discovery of this grid cell network won the 2014 Nobel Prize in Medicine or Physiology to John O'Keefe, May-Britt Moser and Edvard I. Moser, "*for their discoveries of cells that constitute a positioning system in the brain*" (Nobel Prize, 2014). This recently-discovered network of *entorhinal grid cells* activates different patterns depending on how we move. The foremost function of this grid cell network located in the EC is to keep track of our location in a mental map that allows us to navigate through space even without actual visual input cues.

It has been suggested that AD induces the dysfunction of entorhinal grid cells in the EC. People at risk of AD have been found to have lower activity of these grid cells. Dysfunctional EC grid cells seem to explain the spatial disorientation experienced by patients suffering from AD. As a result, the ability of a person to navigate a spatial environment, such as a Virtual Reality (VR) spatial maze, can be used to predict his/her likelihood of developing AD (Kunz et al., 2015).

The possibility of using EC dysfunction as a prognostic tool of preclinical AD opens up novel ICT-based paths to diagnose AD, especially using VR maze navigation tools. It has already been shown that young adults at genetic risk of AD (that is, those who are APOE-e4 carriers) exhibit reduced grid cell-like representations and concurrently display altered navigational behaviours when placed in VR spatial environments. Such correlated behaviour constitutes at least initial evidence of "*... behaviourally relevant entorhinal dysfunction in humans at genetic risk for AD, decades before potential disease onset*" (Kunz et al., 2015).

Early occurrence of entorhinal dysfunction indicative of AD risk may be discovered by subjecting young adults to object-location memory tasks while

navigating freely in a VR environment. Therefore, such VR-based entorhinal dysfunction detection may be used as an early prognostic marker tool of preclinical AD that could also assist in establishing the start of early treatment. In fact, reducing or making more tolerable entorhinal dysfunction could eventually become itself a new therapeutic goal in the treatment of AD (Kunz et al., 2015).

2.4.5. Trials and models

Perhaps the foremost stumbling block faced by the evaluation of developmental therapies intended for AD and ADRD in general lays on the practical logistic issues involved. The leading difficulties are the complexity of the preclinical trials needed to assess disease progression, as well as the long times required to carry out the trials in a meaningful, scientifically valid, accurate and reliable way. These complications come in addition to the difficult but crucial recruitment of significant numbers of adequate human participants.

In the ambit of pharmacological therapy, preclinical testing trials of potential drug therapies normally use transgenic mouse models, usually based on familial AD mutations. Such models are very useful for trials, but so far they have not been very adept at adequately predicting the clinical efficacy of the tested therapies. This is mostly because the transgenic mice normally used for AD experiments do not necessarily offer a parallel that accurately reflects the human variety of the disease (Lowe, 2016). It is obvious that the existence of better animal models for AD that are more translationally significant to humans would be very helpful. Unfortunately, published literature on the subject seems to indicate that presently existing models probably are not true AD, mostly because of poor reproducibility and difficulty in translating to human AD.

More research on model translation is needed if animal models are to be useful in the process of evaluating diagnostic procedures for AD. It is imperative to be able to establish reliable parallels between human and animal models for any meaningful translation of the findings from animal models to humans.

According to Keene et al., the evaluation of parallels between human AD and animal models should include “... *cognitive impairment with emphasis on spatial learning and memory to distinguish pre-symptomatic and symptomatic mice at specific ages*” (Keene et al., 2016). There happen to be some specific spatial location/navigation cognitive testing procedures, such as the well-known Morris water maze (Laczó et al., 2010, 2012), that seem to be promising candidates for establishing such animal/human model parallels. For any such translationally-able testing procedures to be really useful in practice they should be relatively easy to perform, unmistakably reproducible, and above all utilise standard protocols that are amiable to translation.

2.5. THERAPEUTIC INTERVENTIONS

We loosely use the term “treatment” within the present context of AD and ADRD in a very broad manner to refer to the administration of any pharmacological substance, or any invasive or non-invasive non- pharmacological intervention, whose main purpose is to prevent, delay the onset, cure, stop, slow, reverse, treat the cognitive and behavioural symptoms, or even just to ameliorate the human consequences of the disease, with the ultimate purpose of improving the quality of life (QoL) of AD and ADRD patients and their families.

2.5.1. Pharmacological therapies

Currently there is no preventative or curative pharmacological treatment for Alzheimer's disease. In spite of some recent noteworthy pharmacological therapeutic

accomplishments and other promising research presently underway, as of today, more than a century after the discovery of AD, there are still no significantly effective pharmacological treatments of sufficiently proven efficacy to prevent, cure or delay this incapacitating and devastating disease (Joanette, Hirsch, & Goldman, 2014).

Many drug treatment clinical trials for AD had to be terminated because they were found to be ineffective (Dolgin, 2016). As an example, consider that, according to Katsnelson et al., *“Between 2002 and 2012, 413 clinical trials assessing 214 compounds to treat Alzheimer’s disease yielded just one new approval by the U.S. Food and Drug Administration—a success rate of 0.4%. No new treatments have been approved since 2003”* (Katsnelson, De Strooper, & Zoghbi, 2016). And the few drug therapies that have been approved for AD intervention, all aim to treat the symptoms, not the disease itself (Dolgin, 2016), following the mainstream line of today’s prevailing Alzheimer’s intervention paradigm.

Very few medicines are available that specifically aim at AD. In the USA only four prescription drugs have been approved for AD so far by the U.S. Food and Drug Administration (FDA). They are Donepezil, Galantamine, Memantine, and Rivastigmine (Alzheimer’s Association, 2017b). They are the same as those mostly used in the rest of the world. But none of them is curative. They are all intended to ease AD-associated symptoms. Similarly, there are very few (around ten) experimental pharmacological treatments that are presently being formally and officially tested.

In spite of the disheartening results, researchers continue to feverishly attempt to develop pharmacological therapies that target specific genetic, molecular, or cellular mechanisms apparently inherent to AD, so that the dreadful disease can one day be halted or averted (National Institute of Health, 2016).

2.5.2. Non-pharmacological interventions

Many experts are nowadays advocating the urgent development of low-cost AD approaches that do not require drug research. Thus, interest is quickly growing in generating non-pharmacological interventions for dementia in general and AD in particular. A shift to a broader approach is needed from today's prevailing AD intervention paradigm, which is too constrained around biological, genetic and chemical biomarkers (Garrett & Valle, 2015). Such narrowly focused view inhibits placing more emphasis on the allocation of sufficient financial and human resources for developing and implementing other important factors known to be possible paths to ameliorate the effects of this disease. Experience suggests that other types of interventions, such as lifestyle changes, diet, physical exercise, skill development and retraining, occupational therapy, cognitive training, and mood uplifting, could be useful tools that would postpone or delay disease progression, or at least turn it more manageable (Dolgin, 2016).

Occupational Therapy (OT) has been proposed as one of the possible non-pharmacological intervention for MCI and AD dementia patients, with the aim of preserving a certain level of cognitive and affective functionality, moderating troublesome behaviours, increasing patients' QoL in general, and decreasing caregivers' burden. The short-term efficacy of OT has been very recently investigated and ascertained in patients with dementia by Pimouguet et al (Pimouguet, Le Goff, Wittwer, Dartigues, & Helmer, 2017). They have assessed the effectiveness and possible benefits of OT through Mini-Mental State Examination (MMSE), Disability Assessment in Dementia, Neuropsychiatric Inventory Questionnaire, patients' quality of life (EQ 5D-VAS scale), caregivers' burden (Zarit scale), and knowledge about the amount of informal care. They concluded that "*OT may be an effective intervention to maintain cognition and functionality and to reduce psychiatric symptoms in dementia*

patients. Mild stages of dementia could gain more benefits from OT with regard to functional decline” (Pimouguet et al., 2017).

Non-pharmacological interventions for the aging population are widely viewed as effective and relatively inexpensive means of palliative therapy (Alzheimer’s Association, 2017a) that are thought to be capable of improving, or at least preserving, cognition and memory, and possibly even sensory and motor functions as well. A recent systematic review and meta-analysis of nine studies of non-pharmacologic cognitive intervention in older adults with subjective cognitive decline (self-perceived cognitive decline but clinically normal function) found a small but significant effect of such interventions that can benefit objective cognitive functioning (Smart et al., 2017).

Other studies using novel ICT-based cognitive training interventions that are deployed through traditional computer interfaces (e.g. 2D video displays, specialized game consoles, etc.) (Wang, 2016), smart mobile devices, as well as more sophisticated ICT-based alternatives such as 3D immersive VR (García-Betances, Arredondo Waldmeyer, Fico, & Cabrera-Umpiérrez, 2015; García-Betances, Jiménez-Mixco, Arredondo, & Cabrera-Umpiérrez, 2015) combined with enhanced or augmented reality (AR) (Chicchi Giglioli, Pallavicini, Pedrolì, Serino, & Riva, 2015) interactive environments.

In this broadened view of AD intervention, research must enable and advance the use of the modern means and instruments that modern technology places at our disposal. Efforts should be directed to developing, designing and implementing novel ICT-based tools to enhance or maintain physical and cognitive function by managing AD’s behavioural symptoms, such as sleeplessness, wandering, agitation, anxiety, and aggression, in order to improve the quality of life of patients and their caregivers. According to the US NIH’s National Institute on Aging, “...*treating behavioural*

symptoms can make people with Alzheimer's more comfortable and make things easier for caregivers" (National Institute of Health, 2016). Therefore intervention approaches should focus on slowing or delaying the symptoms of the disease trying to maintain mental function, and managing behaviour in general.

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CHAPTER 3

RESEARCH QUESTIONS AND OBJECTIVES

This chapter focuses on the originally posed research questions that this doctoral thesis is meant to address and on the objectives thereof. They are briefly listed and described in the following sections.

3.1. RESEARCH QUESTIONS

- **Question #1 (RQ1):** Are ICT-based cognitive interventions scientifically regarded as useful tools for evaluation or treatment of the effects of cognitive impairment disabilities in patients with Alzheimer's disease or related dementias (ADRD)?
- **Question #2 (RQ2):** Can the data collected from this type of computerized tools be useful and clinically relevant?
- **Question #3 (RQ3):** Considering the ongoing brain training debate, should R&D efforts in computerized cognitive training (CCT) interventions for ADRD continue to be pursued? Or for that same reason, should such activities be encouraged, supported or funded?
- **Question #4 (RQ4):** Under what conditions can VR-based intervention tools produce significantly effective results for detection or evaluation and for treatment or mitigation purposes of cognitive disabilities in ADRD patients?
- **Question #5 (RQ5):** It is possible to develop a specific set of general methodological guidelines that can be useful for assisting multidisciplinary R&D teams in the task of designing VR-based cognitive evaluation and treatment interventions for ADRD patients, aimed at improving their quality of care (QoC) and quality of life (QoL)?

3.2. OBJECTIVES

3.2.1. General Objective

The overall objective of this doctoral thesis is to facilitate increased use of advanced VR-based platforms specifically intended for dispensing computerized cognitive evaluation and therapeutic interventions to people living with, or at risk of developing, ADRD, to better address their complex cognitive healthcare needs. A methodological design framework to provide guidance to developers of such VR-based cognitive interventions is the ultimate outcome of this objective.

3.2.2. Specific Objectives

- O1.** To establish the scientific validity of ICT VR-based solutions as useful tools for the evaluation and treatment of cognitive impairment disabilities in patients with Alzheimer's or related diseases (ADRD).
- O2.** To ascertain that the data collected from VR-based cognitive evaluation and treatment interventions for ADRD patients is useful and clinically relevant.
- O3.** To identify and assess the strengths and weakness of the applicability of VR-based cognitive interventions for evaluation and treatment of ADRD cognitive disabilities.
- O4.** To assess and establish the role that VR technology can play in the detection, evaluation, treatment and mitigation of the effects of cognitive impairment in ADRD patients.
- O5.** To assess current methodologies and guidelines, users' needs, and possible technological and acceptance barriers specifically related to the use of VR-based cognitive evaluation and treatment interventions for ADRD patients.

- O6.** To propose a systematic methodological design framework to guide multidisciplinary teams in the conception and design of VR-based cognitive interventions for ADRD patients intended for:
- a. reliably and objectively detecting and assessing cognitive impairment symptoms during the early MCI stages of AD, and subsequently monitoring the course of cognitive decline;
 - b. cognitive training of patients to mitigate the effects of ADRD symptoms on their Activities of Daily Living (ADL) and QoL;
 - c. searching for and studying possible AD-associated indicators whose assessment could be implemented in novel VR-based diagnostic and prognostic instrumental procedures to detect and foresee the progression of early signs of AD; and
 - d. providing valuable feedback from the VR-based cognitive intervention, to refine and improve its operation and effectiveness through epistemic iteration, as well as to extend the supporting knowledge base of this technology.

CHAPTER 4

MATERIALS AND METHODS

This chapter describes the methods and materials adopted for addressing the main objective of the present doctoral thesis, as well as for answering the research questions raised in Chapter 3. The proposed methodological approach is comprised of three phases that correspond to the stated research questions and specific objectives. A representation of this interrelation is presented in Figure 4.1.

In order to answer the proposed research questions we embarked on a working methodology that led to the definition of new criteria of well-defined methodologies. The following sections describe the materials and methods used for each phase.

4.1. PHASE 1 - SCIENTIFIC BASIS ANALYSIS

This initial phase involves the preliminary literature-based research and data collection referred to the specific target group of end users, ADRD, as well as involved specialists, and caregivers. This phase is intended to achieve research objectives O1 to O4, by conducting a review and thorough analysis of published specialized research related to ADRD, as well as to ICT-based, and especially VR, neurocognitive interventions. The analysis includes the critical assessment of ICT-based and VR interventions conducted to ascertain their scientific validity, clinical relevance, and possible roles, as tools for improving the QoC and QoL of people living with ADRD. The critical assessment particularly focuses on the diagnostic uses (detection, evaluation, construct discrimination, progression follow up, etc.) of ADRD-specific symptoms, as well as on the therapeutic uses (treatment, training of cognitive abilities, mitigation of symptoms, etc.).

Figure 4.1- Methodological approach scheme

4.1.1. Analysis of relevant research

4.1.1.1. *ICT-based and VR technologies use in ADRD:*

The methodology used may be divided into two main stages: (1) literature search and selection of relevant research work; and (2) categorization of the analysed research. The first stage consists of an initial computer-based on-line not fully systematic literature search, conducted in several high-profile databases, such as: PubMed, Web of Knowledge, IEEExplore, Science Direct, and Google Scholar. Only

peer-reviewed journal articles written in the English language were considered. Because of conciseness, and considering the relative novelty of the field, the search was mostly limited to years from 2000 to the present. However, a few pre-2000 specific articles were included by reason of their historic value or outstanding relevance. References cited by the initially retrieved articles became a secondary source for manual selection, and they were included whenever they contributed significant new information.

VR-based technology studies and applications related to ADRD assessment and cognitive intervention were searched for using the following search terms, and combinations thereof: Virtual Reality, Virtual environments, virtual game, Alzheimer's disease, cognitive impairment, cognitive rehabilitation, and cognitive training.

In addition to the most relevant recent research of VR applications that involve ADRD patients, some other studies aimed at healthy elderly people were included because of their comparative value. Articles dealing with MCI patients were also included since such impairment is often a transition from healthy aging to AD. We excluded those studies and applications where the devices used to interact with the VE were not clearly described. A few articles whose full-text was not easily accessible were also excluded. The second stage of the review consisted of categorizing, for later systematic study and analysis, the retrieved studies and research, according to a predefined classification.

4.1.1.2. Computerized neurocognitive interventions and the brain training controversy:

The analytic narrative presented in chapter 6 is intended to critically scrutinize the subject without pretending to be a rigorous systematic meta-analysis review. Thus, it does not contain an exhaustive and systematic search of all existing literature.

Rather, the choice of relevant works, studies, reports and other documents mentioned is the result of continuous literature survey and manual selection, guided by accrued expertise on the subject. Besides the author's own growing topical knowledgebase archive, sources of information include some of the more usual general scientific peer-reviewed journal data bases, such as PubMed, Web of Knowledge, IEEEExplore, Scopus, and Google Scholar. Other types of general and specific sources, such as science and professional magazines, news bulletins, technical reports, have been routinely consulted whenever relevant to the subject. Web portals of pertinent governmental institutions and non-government organizations and associations, as well as those of some specific for-profit enterprises, were also accessed. Whenever wide-ranging searches were needed, they were conducted using topic-related key-words. Among other terms the following were used: cognitive intervention, computer-based cognitive intervention, cognitive training, brain training, computerized cognitive training, cognitive impairment rehabilitation, MCI, virtual reality, VR. As before, considering the relative novelty of the topic, most references are limited to recent years. Only those that were deemed to be of particular relevance and significantly important for the specific purposes of highlighting, exemplifying or emphasizing the arguments of the narrative were chosen and were cited.

4.2. PHASE 2 – FRAMEWORK CONCEPTUALIZATION

The second and third phases pertain to the proposed Methodological Design Framework. This second phase deals with the interdisciplinary nature of the framework's conceptual definition, and it is intended to accomplish research objective O5. It involves the analysis of current guidelines and recommendations related to ICT and VR design and interaction techniques for easy-to-use solutions, specifically for

elderly and/or AD or related dementias patients; and the assessment of strengths and weakness of current methodologies to conduct ICT-based CT studies.

4.2.1. Analysis of guidelines and recommendations:

We have analysed currently available guidelines and best practice recommendations in order to determine what aspects and issues may be considered as key factors for “ease-of-use” and acceptance of ICT-based technologies (interfaces and interventions) on the part of people with cognitive disabilities. The analysis starts from a general perspective exploration of general purpose VR application software design guidelines and widely implemented user-centred design approaches that determines the basis of any ICT design and development focused on user’s needs, characteristics and limitations. Then, a more specific analysis of current guidelines and best practice recommendations, related to cognitive and physical accessibility for people with cognitive disabilities, was conducted in terms of user interface designs, types of interactions, content, etc. Finally existing strategies and recommendations related to the assessment and evaluation of cognitive intervention programs were studied. In this regard, the guidelines of the “Institute of Medicine Criteria for the Evaluation of Cognitive Training Programs” and the “US NIH’s National Institute for Aging Toolbox® for Assessment of Neurological and Behavioural Function” were particularly analysed to identify best practice suggestions for the evaluation of ICT-based interventions for cognitive disabilities care. The following sub-sections present brief descriptions of such guidelines. Chapter 7 will present a summary of the framework’s guidelines, highlighting those most relevant and essential methodological recommendations that should be taken into account for development and design.

4.2.1.1. User-centred Design

According to user-centred design standard ISO 9241-210:2010 (International Organization for Standardization, 2010), the definition of a user-centred design approach is: “*an approach for systems design and development that aims to make interactive systems more usable by focusing on the use of the system and applying human factors/ergonomics and usability knowledge and techniques.*” Adherence to the principles of this approach in general affords considerable economic and social benefits to users, developers and suppliers that can be summarized as:

- a. Increased productivity;
- b. Reduced training and support costs;
- c. Increased usability and increase accessibility for people with different capabilities;
- d. Improved user experience;
- e. Reduced discomfort and stress;
- f. Improved the definition of functional requirements;
- g. Increased the likelihood of completing a project successfully; and
- h. Reduced product failure risks.

4.2.1.2. Web Content Accessibility Guidelines (WCAG)

The World Wide Web Consortium (W3C) is an international community that develops open standards to ensure long-term growth of the Web. Specifically, within the Web Accessibility Initiative (WAI), several sets of strategies, guidelines, and resources are proposed to make the Web accessible. The working group that specifically deals with accessibility of people with disabilities and publishes the Web Content Accessibility Guidelines (WCAG) is called “the Accessibility Guidelines

Working Group.” This group is divided into major objectives corresponding to following five task forces:

- Accessibility Conformance Testing (ACT) Task Force
- Cognitive Accessibility Task Force (COGA)
- Low Vision Accessibility Task Force
- Mobile Accessibility Task Force
- Silver Task Force

Chapter 7 will present the specific analysis of COGA’s guidelines and recommendations, as well as some important physical and user interface accessibility guidelines from the WCAG task forces.

4.2.1.3. Institute of Medicine Criteria for the Evaluation of Cognitive Training Programs

The Institute of Medicine is an institute created and established by the US National Academy of Sciences with the main aims of serving as an adviser to the US federal government to identify issues of medical care, research, and education regarding public health. The Institute of Medicine, nowadays called the Health and Medicine Division of the National Academies, published in 2015 a set of recommendations and best practices for the evaluation of cognitive training programs (Blazer, Yaffe, & Liverman, 2015). These recommendations and best practices are the result of the extensive assessment of the public health dimensions of cognitive aging, specifically those related to epidemiology, surveillance, prevention, intervention, education, and public awareness. Within these recommendations, five criteria stand up as those that must be followed to evaluate the effectiveness any cognitive training program (Merzenich, 2016)..

The Health and Medicine Division of the US National Academies also places especial emphasis on the importance of homogenising the wide variety of tools and

measurements available for testing cognitive changes, many of which are not even relevant to all activities of daily living. This disparity of methods significantly hinders and complicates the process of assessing and comparing findings and results from different sources. Lack of homogeneity and standardisation in the measurement tools used for cognitive change testing make it harder to demonstrate the transfer of trained skills onto real tasks, and to ascertain how long those skills may last.

4.2.2. Assessment of strengths and weakness

The procedure to identify the strengths and weakness regarding the applicability of ICT VR-based neurocognitive interventions for cognitive disabilities care, follows what is known as a SWOT (Strengths–Weaknesses–Opportunities–Threats) approach that stems from strategic management research conducted in the 1960s and 1970s. Nowadays SWOT is a commonly employed framework in the business world. It provides a methodology for “*analysing the factors that influence a company’s competitive position in the marketplace with an eye to the future*” (Rizzo & Kim, 2005). Its most useful contribution is in identifying the internal and external factor interactions that affect the successful achievement of the goal, as well as serving as a practical instrument to define long-term strategies. The SWOT approach has been applied throughout the years in other domains aside from the business world, such as: healthcare, information & technology services and solutions, urban-renewal projects, career planning, website design, sports programs, academic research centres, etc. (Rizzo & Kim, 2005).

In a general context SWOT can be applied to any attend to accomplish a goal with an expectation of obtaining good outcomes, by taking into account the internal and external factors involved. The SWOT approach specifically refers to the

following important concepts to be considered (Rizzo & Kim, 2005; Team FME, 2013):

- *Strength*: an internal capacity, characteristic or factor that is favourable to allow an entity to achieve its goals.
- *Weakness*: an internal limitation or factor that is unfavourable to progress toward the entity's goals.
- *Opportunity*: an external factor or trend that increases the entity's capacity and/or its effectiveness to achieve goals.
- *Threat*: an external situation or factor that presents an unfavourable barrier to achieving the goals.

Figure 4.2 shows the sketch of SWOT matrix into which the lists of strengths, opportunities, weaknesses, and threads are organized in a way that facilitates the linkage among internal factors and external factors (Bull et al., 2016; Sevkli et al., 2012). Interaction among the elements of this matrix allows to dentine and formulate long-term strategies to achieve the desired goals. There are four types of strategies:

1. Strengths-Opportunities (SO): those that use internal strengths to take advantage of external opportunities.
2. Weaknesses-Opportunities (WO): those that use external opportunities to minimize the severity and improve internal weaknesses.
3. Strengths-Threads (ST): those that use the potential of internal strengths to avoid or mitigate the impact of external threats.
4. Weaknesses-Threads (WT): those that define actions to reduce internal weaknesses and avoid external threads simultaneously.

STRENGTHS	WEAKNESSES
OPPORTUNITIES	THREATS

Figure 4.2 – SWOT matrix

Chapter 7 presents the SWOT analysis matrix used in this work, together with a description of the rationale behind each identified factor.

4.3. PHASE 3 – METHODOLOGICAL FRAMEWORK DEFINITION

This third and last phase deals with the Methodological Design Framework itself. Specifically, this phase deals with the definition of new criteria of well-defined methodologies and good-practices for exploring the applicability of VR in cognitive disabilities care, specifically for people with ADRD. Methodological Design Framework concepts and components that are defined at this phase correspond to the outcomes of phases 1 and 2, indicated in the rightmost column of the methodological scheme chart shown in Fig. 4.1.

Based on the definitions of “methodology” and “framework” from the Oxford English Dictionary, a methodological framework could be defined as an “*underlying structure, conceptual scheme or system which comprehends a set of methods used in a particular field of study.*” Consequently, a methodological framework devised to guide the design, development, and evaluation process of exploratory, experimental, or investigative VR-based cognitive intervention for ADRD care should follow, in a general sense, the basic principles of the Scientific Method.

Within the scope of the present discussion, we could succinctly characterise the aim of the Scientific Method as “*a set of mathematical and experimental techniques employed in the natural sciences for the construction and testing of*

scientific hypotheses” (“Scientific Method,” 2017). Accordingly, the main goal would be to define a structured iterative work process of observations and data gathering aimed at answering scientific questions. This iterative process resembles a “trial and error” type of approach that involves steps to ascertain cause and effect relationships between the scientific questions and the gathered and analysed data, as well as to determine whether the available evidence can be combined into a logical answer (Uribe C., 2015). Figure 4.3 shows the steps of such Scientific Method-based procedure.

Figure 4.3 – Scientific Method steps

In the engineering disciplines the Scientific Method usually translates into the methodology commonly used for the creation of new products, infrastructures, processes, applications, etc. That methodology, which we may call the “creative design process,” is in fact comparatively parallel to the Scientific Method. Table 4.1 shows a schematic comparison of both procedures. The research processes followed for developing advanced technologies usually are an intertwined combination of both schemes. History is full with remarkable examples of this intense symbiosis between science and engineering. Galileo Galilei, Michel Faraday, and Nicola Tesla are three classic examples. Other more modern expressions of such science-engineering synergy are the discoveries and developments in the area of electronics and telecommunications engineering that have received the Nobel Prize in Physics: 1909 = wireless telegraphy (Guglielmo Marconi and Karl Ferdinand Braun); 1956 = discovery of the transistor effect (William Bradford Shockley, John Bardeen and Walter Houser Brattain); 1973 = tunnel barriers in semiconductors and superconductors (Leo Esaki, Ivar Giaever and Brian David Josephson); 2000 = semiconductor heterostructures (Zhores I. Alferov and Herbert Kroemer); 2000 = integrated circuits (Jack S. Kilby); 2009 = charge-coupled devices (Willard S. Boyle and George E. Smith); 2009 = transmission of light in fibres for optical communication (Charles Kuen Kao); 2010 = Graphene (Andre Geim and Konstantin Novoselov); 2014 = efficient blue light-emitting diodes (Isamu Akasaki, Hiroshi Amano and Shuji Nakamura).

Scientific Method	Creative Design Process
Formulate the question	Define the problem
Do background research (previous theories)	Do background research (state of the art)
Formulate the hypothesis	Describe the product
Identify the variables	Specify the requirements
Design the experiment	Design alternative solutions
Establish the procedure to follow	Choose and develop prototype of the more suitable alternative
Test the hypothesis with the experiment	Test the prototype
Analyse the results and if necessary redesign the experiment	Analyse the results and if necessary redesign the prototype
Draw conclusions	Draw conclusions
Communicate results through scientific journal publications	Announce results through technical reports, journal publications, patents or demonstrations

Table 4.1 - Schematic comparison of the Scientific Method and the Creative Design Process

The definition of the proposed methodological design framework's conceptual scheme is rooted in the previously described outcomes and the knowledge obtained from published research examination and SWOT analysis, taking into consideration the guidelines and good-practices required to design, develop and test ICT-based technology solutions aimed specifically for people with cognitive disabilities. The process used to construct the framework structure, including the concepts and components, was mostly based on the essential principles of Latham's (Latham, 2014) definition of "The Research Canvas" and "Research Methods Framework."

4.3.1. The Research Canvas

Figure 4.4, presents the general structure of the research canvas proposed by Latham (2014), in which nine components are presented in a sequence, but are also iteratively interrelated.

Figure 4.4 – Latham’s Research Canvas: A Framework for Designing and Aligning the “DNA” of Your Study

The nine general components of the research canvas are (Latham, 2014):

1. *Problem*, identifies a condition, difficulty or challenge to be solved and the current inability to solve it, based on existing knowledge.
2. *Purpose*, presents a statement of "why" the research is being conducted and the new knowledge or solution it will provide. It is based on the knowledge gap identified in the problem statement. Some key components of the purpose statement could be: a dissatisfaction with the current level of knowledge or performance, the vision of the research, the determination of what type of knowledge that will be produced, and the identification of the expected outputs.
3. *Questions*, identify answerable inquiries regarding a specific concern or issue in order to fulfil the purpose. There are two types of questions: quantitative questions that refer to measurable variables, and

qualitative questions that inquire into the nature of something and ask how it occurs or works.

4. *Conceptual Framework*, identifies the key constructs (e.g. trust, satisfaction, commitment, etc.) and variables (independent, dependent, etc.) from the questions, the relationships between them and the context factors present. A conceptual framework is represented graphically or in narrative. If the constructs, variables and relationships are measurable using quantitative methods, it can be called a “theoretical framework.”
5. *Literature Review*, identifies and summarises current (pertinent time period depends on specific topic) knowledge, key findings and contributions found in the related and associated literature, regarding the components, variables and relationships identified in the conceptual framework.
6. *Overall Approach*, defines the complete approach of the research, in terms of its methodology and specific design (e.g. case study). It depends on the problem, purpose and research questions, as well as the type of constructs, and variables defined (e.g. measurable or not measurable). To identify the overall approach of the research Latham (2014) recommend the use of a “research arc” (Figure 4.5) in which the relationship between the empirical knowledge and the applicable approach is displayed.

Figure 4.5 –Research Arc (Source: Latham, 2014)

7. *Data Collection*, determines the methods, instruments, and sources to measure the study variables, as well as the sampling strategy.
8. *Data Analysis*, deals with the description or measurement of the constructs, variables, and context factors by analysing their relationships. The methods available for analysis are determined by the type and level (nominal, ordinal, interval, and ratio) of the collected data.
9. *Drawing Conclusions*, collates all the findings and their implications for current theory and practices into a cogent conclusion and discussion. It also describes the limitations of the study associated with the conclusions.

The general components are organized into two groups that Latham called the “T” or foundation and the “U” or methodology. The “T” group includes the problem, purpose, research questions and conceptual framework (green cells in Figure 4.4). The “U” group includes the literature review, overall approach, data collection, data analysis, and drawing conclusions (blue cells in Figure 4.4).

Each component is related to others. This relationship depends on the links and the level of consistency that is needed for a general view of the research design and the methodology to guide the process. The design process starts at the problem and ends with the solution. As Figure 4.4 shows, a change in one component requires to go back to the definition of the conceptual framework in order to re-define the key factors and variables, and to ensure consistency between all the components and the conceptual framework. If this consistency is not guaranteed, revision of the conceptual framework the specific component is recommended. The rest of the component relations can be summarized as follows (Latham, 2014):

- *A Problem* (knowledge gap) produces a *Purpose*;
- Answers to *Questions* fulfil the *Purpose*;
- *Conclusions* produce new knowledge to solve the *Problem*;
- Concepts and variables to generate *Questions* are focused on previous knowledge (*Literature Review*);
- Findings from *Data Analysis* lead to new *Conclusions*;
- The *Overall Approach* depends on the methods and variables defined in the questions and the previous knowledge (*Literature Review*);
- The *Data Collected* and the questions influence the *Data Analysis*;
- The defined *Overall Approach* leads to the *Data Collection* methods.

4.3.2. Research Methods Framework

Based on the research canvas, Latham defined a “Research Methods Framework” (Latham, 2014) to help researchers design a custom research methodology for their particular projects. As shown in Figure 4.6, this framework follows the structure of the general components of the research canvas, but opens the way to the process of developing a good research design by specifying concepts

related to research approaches. Along with Latham's approach, we take into consideration other very important component aspects that significantly influence the design, development and testing processes of ICT-based solutions for people with ADRD. These component are closely related to: (1) personal user needs in terms of comprehensibility, accessibility, usability, safety, etc.; (2) type of technology used; (3) the interaction techniques involved; (4) privacy and data security; and (5) ethical and legal aspects.

Figure 4.6— Research Methods Framework according to Latham.

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CHAPTER 5

ICT-BASED AND VIRTUAL REALITY TECHNOLOGIES USE IN ALZHEIMER'S DISEASE AND RELATED DEMENTIAS

5.1. BACKGROUND

In recent years many researchers have started to focus their attention on the prevention and treatment aspects of Dementia (Borson et al., 2013; Clare et al., 2013; Cordell et al., 2013; Monteagudo Peña, 2012). Being as it is a currently critical public health challenge, early dementia treatment calls for the development and implementation of novel actions. Nonpharmacological interventions, such as cognitive training and behavioural interventions (Alzheimer's Association, 2013), for memory disabilities have gained much attention in recent years (Cotelli, Manenti, Zanetti, & Miniussi, 2012). Theories of brain plasticity mechanisms (e.g. axonal sprouting, glial cell activation, denervation super-sensitivity, and metabolic changes), as well as recent findings about the ability of the brain and nervous system to reconstruct new cellular synapses as a result of interaction with enriched environments, have opened up the way to new and increasing research activity in the area of memory rehabilitation (Cotelli et al., 2012; Morganti, 2006). Nonpharmacological therapies are intended to maintain cognitive function or to help the brain compensate for impairments so that the QoL can be improved by reducing behavioural symptoms such as depression, apathy, wandering, sleep disturbances, agitation, and aggression (Alzheimer's Association, 2013). There is evidence that some specific nonpharmacological therapies may improve or stabilize cognitive function in the performance of daily activities (Olazarán et al., 2010).

5.1.1. Cognitive Training

Recent brain plasticity theories and findings about the nervous system's ability to reconstruct cellular synapses as a result of interaction with enriched environments, have spurred new research about memory rehabilitation. Consequently, non-invasive non-pharmacological cognitive training (CT) interventions have gained increasing attention in recent years. Studies have substantiated the effectiveness of brain plasticity theories and cortical activation in psychological aging CT (Basford & Malec, 2015; Cotelli et al., 2012; Garcia-Betances, Jimenez-Mixco, Arredondo, & Cabrera-Umpierrez, 2014; Grady & Craik, 2000).

Cognitive training programmes refer to “*any non-pharmacologic intervention designed to improve cognitive functioning, regardless of mechanism of action*” (Sitzer & Jeste, 2006). This concept has been used in several rehabilitation domains such as: aphasia, unilateral spatial neglect, attention disorders, memory, apraxia, acalculia (disorders of number processing and calculation), etc., and have shown evidence about effectiveness of cognitive rehabilitation (Cappa et al., 2005).

Functional neuroimaging yields evidence that certain cortical areas of older adults display greater or lesser activity depending on the task performed and the conditions to which they are exposed (Buldú et al., 2011; Celone et al., 2006; Grady & Craik, 2000; Thivierge, Simard, Jean, & Grandmaison, 2008). CT based on this brain plasticity concept has been found to improve cognitive functions that can last for up to 5 years after the intervention (Cotelli et al., 2012), showing evidences of less decline in self-reported Instrumental Activities of Daily Living (IADL) (Brunelle-Hamann, Thivierge, & Simard, 2015; Rebok et al., 2014; Willis et al., 2006) and have an impact on slowing the age-related decline process by maintaining and enhancing the cognitive ability of older adults (Kwok et al., 2013). Recent studies have also confirmed such improvements through the use of computerized cognitive training

(CCT) programs, offering further evidence of the beneficial effects of CT on memory and attention (Smith et al., 2009; Zelinski et al., 2011). The potential usefulness of non-invasive nonpharmacological CT intervention in the early stages of ADRD has been already accredited by various studies reported in the specialized literature (Brunelle-Hamann et al., 2015; Cipriani, Bianchetti, & Trabucchi, 2006; Cotelli et al., 2012).

In spite of the fact that MCI and early-stage dementia represent key periods for providing effective patient intervention, CT is not being routinely offered for such patients (Hampstead, Sathian, Moore, Nalisnick, & Stringer, 2008; Thivierge et al., 2008). On the other hand, most of today's CT interventions in ADRD are mainly focused only on episodic memory intervention. As there is no single specific approach or method for effective CT, several studies have confirmed the efficacy of CT techniques in training individuals with MCI (Belleville, 2008; Schimdt B, Forlenza, & Sanches Y, 2009) and dementia using different techniques, or focusing the training on different domains of cognition, such as learn, relearn, keep over time, and apply information to everyday contexts. Cognitive training also helps to develop strategies to compensate for memory impairment and to adjust the environment to reduce memory demands (Seelye, Schmitter-Edgecombe, Das, & Cook, 2012). There is also evidence of the efficacy of teaching visual or semantic mnemonics to improve episodic memory in individuals with early-stage Dementia (Rozzini et al., 2007; Thivierge et al., 2008). Analysis of CT experiences indicates that techniques such as Errorless Learning and Spaced Retrieval are promising procedures for memory training in patients with AD (Belleville et al., 2011; Cotelli et al., 2012). Clare et al. extended previous studies of CT interventions based on errorless learning principles in which they found new evidence of the effectiveness of this kind of intervention for early-stage AD patients (Clare, 2010; Clare, Wilson, Carter, Roth, & Hodges, 2002).

5.1.2. Computers in Neuropsychology

The use of computers in psychological testing began over a quarter of century ago (Riva, 2000). Today new software technologies are being gradually introduced into the domain of dementia care to assist patients and their families, mainly by providing memory aids and educational support. A growing number of research, development, and innovation (R&D+i) undertakings have focused in recent years on ICT applications intended to help the dependent elderly population, their families, and their caregivers (Cipriani et al., 2006; “Europe 2020,” n.d.). Several fields, such as Domotics, Ambient Intelligence (AmI), e-services, and telemedicine, are examples of this trend. A few computer-based CT exploratory programs have been carried out aimed at elderly people with Dementia (Cipriani et al., 2006; Hofmann et al., 2003; Monteagudo Peña, 2012; Smith et al., 2009). There are also several projects and research studies developed in the last 2 decades where computer-based interventions were suggested for memory training and CT of elderly people with MCI and early-stage dementia. Such incipient training intervention actions already reveal the potential benefits for function improvement in select cognitive tasks such as face–name association, memory, attention, list recall, IADLs, and so on (Belleville et al., 2011; Boger et al., 2006; Cipriani et al., 2006; Monteagudo Peña, 2012).

Recently, the Lancet Commission on Dementia Prevention, Intervention, and Care met to consolidate existing knowledge on dementia care, and to put forward pertinent recommendations for its management (Livingston et al., 2017). The Commission of 24 scientists was led by Gill Livingston, Professor of Psychiatry of Older People at the University College London, and in partnership with the Alzheimer’s Society, the Economic and Social Research Council, and Alzheimer’s Research UK. Beyond general suggestions about prevention by managing potentially modifiable lifestyle factors in early and middle age that could delay or reduce the risk

of developing dementia, providing individualized care, protecting the patient against possible risks and dangers, taking care of concomitant neuropsychiatric symptoms, etc., this Commission also advocated the use of technological interventions to advance care delivery, as long as these interventions improve care without replacing social contact or increasing risks for people with dementia and their families.

5.2. ICT-BASED THERAPEUTIC COGNITIVE TRAINING

Videogames, serious games and computerised cognitive training applications may have various features in common, but in principle belong to different categories. They are all based on computerized platforms (mainframe, personal computer, smartphone, tablets, etc.) with 2-D or 3-D image display devices (monitor screen, VR head-mounted display (HMD) goggles), that are operated through user interfaces (game controller) and generate at least visual and audio responses, but eventually also kinetic and other sensations (Vaportzis, Martin, & Gow, 2017). Videogames are designed primarily for entertainment, whereas serious games are usually meant to convey information or learning experiences beyond genuine entertainment, for job training or skill improvement, and for educational and remote learning purposes. On the other hand, computerized cognitive training (CCT) provides cognitively challenging tasks to exercise various cognitive domains of the human mind.

Interactive CCT applications can be presented to the user through the traditional 2D video displays of game consoles (Wang, 2016) or smart mobile devices. However, more sophisticated alternatives for CCT, such as 3D immersive Virtual Reality (VR) (García-Betances et al., 2015a; García-Betances et al., 2015b) are available. VR also can be combined and enhanced with Augmented Reality (AR) capabilities (Chicchi Giglioli, Pallavicini, Pedrolì, Serino, & Riva, 2015) to create more interactive and Mixed Reality (MR) environments. There are also other

promising ICT-based next-generation ideas, such as multisensory feedback and holographic 3D vision, which are constantly being developed, improved and made available.

A recent quality assessment review and meta-analysis of twelve CCT interventions (García-Casal et al., 2016) confirms that although CCT can produce moderate beneficial effects on cognition and anxiety, and small effects on depression, there seems to be still insufficient evidence to clearly demonstrate that these interventions can significantly improve activities of daily living. Nevertheless, the study does indicate whether the results of CCT interventions are significantly more beneficial than those from non-computer interventions (García-Casal et al., 2016).

Another systematic review and meta-analysis investigated the efficacy of using CCT in depressive disorders (Motter et al., 2016). The study's search from 2007 to 2014 found a total of nine randomized controlled trials (RCT) that met PRISMA's high quality guidelines for systematic reviews and meta-analyses (Moher, Liberati, Tetzlaff, Altman, & Group, 2009). Evaluation of those trials indicates that CCT produces positive effects of diverse significance on domains related to depressive symptoms, daily functioning, attention, working memory, and global functioning; whereas executive functioning and verbal memory do not appear to have experienced significant improvement. Analysis of a more recent systematic review (Smart et al., 2017) of nine trials with older adults with self-perceived cognitive decline, but clinically normal function, indicates small but significant effects that could benefit objective cognitive functioning.

Another recent systematic review and meta-analysis examined seventeen CCT research trials conducted over the last twenty years on older adults with MCI or dementia (Hill et al., 2016). The analysis proves that CCT can lead to significant improvement in global cognition, memory, learning and attention and psychosocial

functioning, including mood, self-perceived quality of life, and depressive symptoms. However, the effects on other domains, such as executive function and processing speed, were not found to be significant. This study provides a noteworthy hint to keep in mind: it is that the effectiveness of CCT seems to be weak in people who already have been clearly diagnosed with dementia. But perhaps the most important finding brought to light by this study is that the evidence of treatment effectiveness that does exist comes predominantly from those trials that were done using immersive type technologies. Immersive VR-based interventions designed for cognitive performance testing, but also for training, of a wide variety of behavioural competencies essential for everyday executive function, are better tools than their more traditional paper-and-pencil counterparts, because they can provide specific ecologically realistic and relevant environments for the intervention. The validity of an immersive VR-based version of the classic Trail Making Test (Salthouse, 2011) was recently demonstrated, by proving that the immersive VR version measures the same cognitive construct as the standard pen-and-paper test (Plotnik et al., 2017).

Such preliminary results suggest that there is already sufficient evidence to warrant to proceed to clinical implementation of CCT. Meanwhile, research should continue to find new ways to improve its effectiveness, so that CCT may eventually be able to provide substantial help in the global fight against dementia (University of Sydney, 2016).

Having a strong motivation to maintain treatment engagement seems to be of paramount importance for the success of CCT, as has been demonstrated by experience. CCT provides the best benefit when it incorporates motivational strategies to enhance treatment engagement in the cognitive therapeutic environment. This has been amply corroborated, among others by a recent study about CCT for older adults with subclinical cognitive decline (Gooding et al., 2016).

The combination of non-invasive ICT-based interventions, such as CCT, with other types of neurotechnological tools or direct interventions is an effective strategy to enhance the effectiveness of ICT-based therapeutic cognitive applications. For example, a minimally invasive direct intervention, using transcranial magnetic stimulation (TMS), was recently applied in combination with CCT to a small group of AD patients (Nguyen et al., 2017). Analysis of the results of that experience suggests that patients can clearly benefit from such combined procedures in the domains of cognitive performance, apathy and dependence, and that the effects persist in the long term.

Perception and acceptance by older patients of new ICT-based interventions for ailment treatment have been frequent subjects of study. Contrary to the common assumption that older people tend to be fearful or anxious of using new or unknown technology, most studies indicate a high rate of acceptance of such new techniques by older people (Kujawska, 2016). Nonetheless, it is still important to consider acceptance aspects when designing accessible ICT-based applications. A study carried out by us about ICT usage by people with aging- and disability-derived functional impairments analysed ICT-based applications to identify relevant cognitive functions involved in accessibility (García-Betances, Cabrera-Umpiérrez, Ottaviano, Pastorino, & Arredondo, 2016; Urwyler et al., 2017). Results showed that using cognitive virtual user models allows to integrate cognitive and perceptual aspects during the design and testing process to make more accessible ICT-based applications and services.

The Lancet Commission on Dementia Prevention, Intervention, and Care has divided existing technological tools for dementia health-care into five general categories (Livingston et al., 2017). We summarise them here because they can provide very useful guidance for clearly classifying the existing broad spectrum of possible ICT-based interventions:

- I. Diagnosis and neuropsychological assessment.
 - a. Computerized neuropsychological cognitive assessment
 - b. Wearable motion sensors
 - c. Virtual Reality (VR)-based assessment of cognition and/or activities of daily living (ADL).
- II. Monitoring of vital signs and changes in the health status and environment:
 - a. Environmental sensors.
 - b. Physiological sensors.
- III. Assistive applications:
 - a. Cognitive aids, including cognitive training (CT).
 - b. Assistance with ADL: reminding and prompting devices, and robots.
 - c. Personal safety: electrical outlet and gas shut-off devices, water temperature sensors, wireless alarms, etc.
- IV. Companionship, and social activities:
 - a. Suitable communication systems to reach care-givers and family.
 - b. Robotic pets
 - c. Activity technology to deliver music, messages, images, and video.
- V. Support for care-givers:
 - a. Telemedicine for communication and data sharing with specialists.
 - b. Web-based information and virtual assistance tools to support care-givers.
 - c. Care-giver access to online support groups.

5.3. VIRTUAL REALITY IN NEUROPSYCHOLOGY

Since the introduction of the use of computers for psychological testing over a quarter of a century ago (Riva, 1998), several studies have emphasized the use of

virtual environments (VEs) and their ecological validity for neuropsychological assessments (Campbell et al., 2009; Parsons, 2015a; Spooner & Pachana, 2006; Tarnanas et al., 2013). VR, a recent branch of ICT, has been suggested for use in some areas of neuropsychology (Coyle, Traynor, & Solowij, 2015; Lesk, Shamsuddin, Walters, & Ugail, 2014; A.A. Rizzo & Kim, 2005; Albert A Rizzo et al., 2001; Schultheis, Himmelstein, & Rizzo, 2002; Shah et al., 2015). Treatment of phobias, stress, and anxiety are characteristic examples of current VR applications in psychotherapy (Esteves Moreira da Costa & Vidal de Carvalho, 2004; Fornells-Ambrojo, Freeman, Slater, & Swapp, 2015; Gregg & Tarrier, 2007; Hartanto et al., 2014; McCann et al., 2014; Paliokas, Tsakiris, Vidalis, & Tzovaras, 2014; Riva, 2005; Smahaj & Prochazka, 2014).

Other helpful medical uses of VR are surgical training, post-stroke intervention, musculoskeletal recovery, pain mitigation, etc. (Gervasi, Magni, & Zampolini, 2010; Haque & Srinivasan, 2006; Imam & Jarus, 2014; Lohse, Hilderman, Cheung, Tatla, & van der Loos, 2014; Pompeu, Alonso, Masson, Pompeu, & Torriani-Pasin, 2014; Snyder, Vandromme, Tyra, Porterfield, & Clements, 2011; Trost & Parsons, 2014; Tsoupikova et al., 2015). The production of VR-based applications intended to maintain or improve the general health and wellness of the elderly is constantly growing. An example is the recent Virtual Rehabilitation (VRRehab) system developed for health promotion, rehabilitation, and injury prevention for the older population (Campelo, Hashim, Weisberg, & Katz, 2017).

Emerging VR applications today address the challenge of diagnosis and cognitive training of MCI and ADRD patients, concentrating on navigation and orientation, face recognition, cognitive functionality, and other Instrumental IADL (Jekel et al., 2015). VR exposes cognitively impaired patients to computer-generated VEs providing a sensation of “presence” or “being there,” for the patient to interact

with in a multisensory fashion through quasi- naturalistic real-life-like stimuli. As we and others have noted (Garcia-Betances et al., 2014; Baus & Bouchard, 2014; Riva, 1998), VR offers the possibility of performing activities, tasks, and tests in VEs adaptable to various characteristics and needs of individual patients, through the use within a VE of several perception aspects of psychophysics, mainly visual, tactile, and kinesthetic perceptual sensations.

A characteristic of VR, which is very helpful for ADRD applications, is the high interaction level that is possible to achieve in a safe VE. Depending on the specific type of VE, patients may interact from an egocentric or an allocentric point of view (Weniger, Ruhleder, Lange, Wolf, & Irle, 2011). The role of egocentric and allocentric abilities in AD have been reviewed by Serino et al. (Serino, Cipresso, Morganti, & Riva, 2014). The devices and stimuli that are used will ultimately determine the level of interaction. A growing number of devices is available today for human interaction (e.g., joysticks, gloves, surfaces, etc.), as well as for stimuli presentation in VEs (e.g., screens, 3D head-mounted displays (HMDs), audio headsets, speakers, etc.)

5.3.1. Virtual Reality in Cognitive Training

As a novel branch of ICT, VR has been suggested not too long ago for use as part of a therapeutic strategy in medical specialties in general, and in particular in the area of neuropsychology. This idea is founded on the fact that the use of perceptual sensations within simulated VR-based immersive and interactive real-life scenarios provides the ability to perform tests in an adaptive environment that can be adjusted to various patients' needs (Optale et al., 2010; Riva, 2000).

VR systems used for therapy have been explored already in several areas, such as brain damage, post-stroke intervention (Lledó et al., 2016; Moraes, de Andrade, &

Paiva, 2016), musculoskeletal recovery, etc. (Gervasi et al., 2010; Rose, Brooks, & Rizzo, 2005; Tost et al., 2009). A recent systematic review of randomized controlled trials evaluated the utility and efficacy of innovative VR-based interventions in pain management, eating disorders, and cognitive and motor rehabilitation in patients admitted to hospitals or rehabilitation centres (Dascal et al., 2017). Immersive VR environments have been used also for neuropsychological assessment (NA) and cognitive rehabilitation (CR) therapies such as: phobias, stress, anxiety, exercise, memory problems, and schizophrenia (Buss, 2009; Esteves Moreira da Costa & Vidal de Carvalho, 2004; Garcia, Kartolo, & Méthot-curtis, 2012; Gregg & Tarrier, 2007; Optale et al., 2010; Parsons, 2015b; Riva, 2005; Albert A Rizzo, Buckwalter, & van der Zaag, 2000; Tost et al., 2009; “Virtualware Group,” n.d.)

Research on the potential of using VR continues to be actively pursued by several groups and laboratories. They focus mainly on cognitive processes, including attention, executive functions, memory (Optale et al., 2010), motor rehabilitation (Tost et al., 2009), motor tracking (Lloréns et al., 2015), special abilities (Parsons & Rizzo, 2008b), and spatial orientation (Kober et al., 2013). VR scenarios have been also designed for testing IADL, including wheel chair navigation (Albert A Rizzo et al., 2000). The VR systems and applications for MCI and ADRD patients that have been developed in recent years have proved to be a promising technology for improving the feasibility and effectiveness of attention bias and executive function CT for the treatment of appetitive behaviour disorders (Forman et al., 2017). Likewise, as we already pointed out (García-Betances, Jiménez-Mixco, Arredondo, & Cabrera-Umpiérrez, 2015) VR offers distinct advantages for use in neuropsychological interventions because it engages one or more psychophysical systems that are vital for cognition: the visual, auditory, haptic, kinaesthetic, and eventually even olfactory sensory perceptions (García-Betances, Jiménez-Mixco, et

al., 2015; Riva, 1998). Additionally, VR-based interventions may be designed for both allocentric and idocentric use, in non-immersive as well as immersive VE modalities.

More unambiguous evidence is needed to fully ascertain the benefits of using VR systems for cognitive rehabilitation of patients with MCI and dementia (Garcia et al., 2012). Some feasibility studies done on the use of this type of systems with such patients have not provided sufficient scientifically solid evidence of significant improvements, and instead have pointed out some instances of VEs simulator acceptance problems (Flynn et al., 2003). On the other hand, there are differing reports that indicate that patients feel a sense of control and enjoyment while interacting with the VEs (Flynn et al., 2003). Some concur in recognizing the benefits of using suitable VEs for cognitive rehabilitation of early stage dementia patients (Buss, 2009; Morganti, 2006). The ability of older people to navigate in a 3D virtual environment and the potential problems for them in terms of interaction, simulator sickness, and well-being also have been studied (Lange, Rizzo, Astur, & Parsons, 2007; Shamsuddin, Ugail, Lesk, & Walters, 2012). Most evidence indicates that people with dementia do not experience significant problems using VR technology, which comes to confirm the feasibility of using VR systems and immersive VEs with such patients.

VR systems are being tried to address diverse treatments applications for MCI and Dementia patients, such as navigation and orientation (Buss, 2009; Cushman, Stein, & Duffy, 2008; Garcia et al., 2012; Morganti, 2006), face recognition (Boggio et al., 2011), cognitive functioning (Buss, 2009; Optale et al., 2010; Parsons & Rizzo, 2008a, 2008b), as well as other IADL (Imbeault, Bouchard, & Bouzouane, 2011; J. Lee et al., 2003; Thivierge et al., 2008). The potential usefulness and exceptional opportunities of VR as an ideal ICT tool for testing and cognitive training of patients

in the early stages of AD has been already ascertained by many studies, as reported in the specialized literature (Cotelli et al., 2012; Déjos, Sauzéon, Falière, & N’Kaoua, 2011; Gregg & Tarrier, 2007; Man, Chung, & Lee, 2012; Schultheis et al., 2002; Yamaguchi, Foloppe, Richard, Richard, & Allain, 2012). However, the regular use of VR-based training technology for MCI and Dementia rehabilitation still requires broader and deeper study and research. The development of VEs that are adaptable, friendly and easy to interact with, and especially tailored for cognitive training of MCI and Dementia patients, is a must for viable VR-based cognitive rehabilitation processes and to maximize their effectiveness. Well designed and soundly described clinical protocols, properly controlled trials, and long term follow ups, are indispensable to generate reliable knowledge about the real efficacy of VR systems use in MCI and Dementia patient rehabilitation (Gregg & Tarrier, 2007; Morganti, 2006). The reasons for the still low adoption in clinical settings of VR technologies for rehabilitation have been analysed and discussed in a recent study (Glegg & Levac, 2017). The result is a series of useful strategies and recommendations for addressing the known barriers and facilitators faced by the clinical adoption of VR.

The next section will illustrate representative state of the art examples of the most significant types of VR applications, indicating the potential advantages of using VR technology for implementing innovative tools to support diagnostic assessment and cognitive training in ADRD.

5.4. CATEGORIZATION OF VR APPLICATIONS FOR ADRD

VR-based systems that are specifically designed for ADRD interventions can be classified, as schematically represented in Figure 5.1, according to several different criteria:

1. The kind of intended purpose (e.g. assessment and diagnosis, cognitive treatment, patient education, caregivers' training, etc.);
2. The type impairment feature it is focused on (e.g. spatial impairment, memory deficit, etc.);
3. The type of methodology employed (e.g. tasks, games or activities);
4. The kind of virtual environment; and
5. The type of interaction technique (e.g. full-immersive, semi-immersive, non-immersive, passive or active interaction, etc.).

Figure 5.1 - Categorization of VR applications used in AD and other related cognitive disorders.

The pursuit of future advances beyond present state of the art of VR applications for ADRD needs to build upon a deep comprehension of recent and ongoing VR developments. Such understanding essentially consists of scrutinizing and comparing design and operation specificities that aim at fulfilling the intended purpose of the particular ADRD application. Operational specificities such as the specific techniques used for patient interaction. A useful starting point, particularly

regarding design methodology type and immersion level, is **¡Error! No se encuentra el origen de la referencia.**, which lists representative current VR applications for ADRD and briefly classifies them according to their intended purpose and interaction technique.

5.4.1. Intended Purpose

Intended purpose refers to the goal for which a particular application was intentionally designed. We have identified three main types of goals among the various recent or current VR systems. They can be succinctly described as: (1) Assessment and diagnosis; (2) Cognitive treatment or therapy; and (3) Caregivers' training. Intended purposes are indicated in **¡Error! No se encuentra el origen de la referencia.**

An possible ancillary goal was proposed by Riva et al. (Riva et al., 2009) regarding the use of VR systems as tools for designing new applications. They developed “Neuro VR,” an open-source VR platform for use in clinical psychology and neuroscience assessment and treatment, which allows non-expert users, such as therapists and researchers, to adapt pre-existing VEs to specific clinical or experimental settings (Riva et al., 2011).

5.4.2. Focal Aspects

Most recent research has focused on certain specific aspects of ADRD cognitive impairment that are generally deemed to be most relevant for VR-based diagnostic and training purposes. They may be roughly summarized as follows:

- *Attention* (Anguera et al., 2013; Kalová, Vlček, Jarolímová, & Bureš, 2005; Manera et al., 2016);
- *Executive functions* (Tarnanas et al., 2013; Tarnanas, Tsolaki, Nef, Müri, & Mosimann, 2014; Yeh, Chen, Tsai, & Rizzo, 2012);

- *Memory*, comprising: non-verbal episodic memory, allocentric and egocentric spatial memory, temporal order memory, prospective memory, short-term and working memory, etc. (Bellassen, Igloi, de Souza, Dubois, & Rondi-Reig, 2012; Burdea et al., 2013; Burgess, Trinkler, King, Kennedy, & Cipolotti, 2006; Kalová et al., 2005; J. Y. Lee et al., 2014; Optale et al., 2010; Shamsuddin et al., 2012; Tarnanas et al., 2013; Weniger et al., 2011; Yeh et al., 2012);
- *Orientation*, specifically: allothetic, visuospatial, wayfinding, spatial navigation, topographical disorientation, etc. (Burgess et al., 2006; Cogné et al., 2016; Cushman et al., 2008; Hort et al., 2007; Kalová et al., 2005; Lange et al., 2007; Nedelska et al., 2012; Zakzanis, Quintin, Graham, & Mraz, 2009);
- *Executive functions and Instrumental Activities of Daily Living (IADL)* (Allain et al., 2014; Buss, 2009; Hofmann et al., 2003; J. Lee et al., 2003; Lozano, Gil-Gomez, Alcañiz, Chirivella, & Ferri, 2009; Tarnanas et al., 2013, 2014; Van Schaik, Martyr, Blackman, & Robinson, 2008; Yeh et al., 2012).

The importance of the above mentioned specific cognitive aspects of ADRD is firmly justified by the accumulated knowledge on the subject, which may be readily consulted in the cited references.

Some intervention approaches look at more than one of the above mentioned aspects for better assessment. Examples of this combined focus are: (Weniger et al., 2011),(Shamsuddin et al., 2012),(Cushman et al., 2008),(Kalová et al., 2005),(Burgess et al., 2006), (Bellassen et al., 2012),(Hort et al., 2007),(Zakzanis et al., 2009),(Nedelska et al., 2012),(Jan Laczó et al., 2009),(Plancher, Tirard, Gyselinck, Nicolas, & Piolino, 2012). Likewise, a combination of more than one aspect may be

used for more effective training tools (Anguera et al., 2013; Buss, 2009). Frequently, memory and attention are combined with navigation, because navigational impairment is a common manifestation of AD that implies disorders of spatial cognition, spatial memory and orientation. For example, in Bellassen et al. (Bellassen et al., 2012), they assessed temporal order memory through active navigation (spatiotemporal navigation) to obtain a sensitive and specific behavioural non-verbal marker of mild AD. Lee et al. (J. Y. Lee et al., 2014) evaluated spatial memory in amnesic MCI (aMCI) patients based on the results of a VR-based virtual route learning environment called virtual radial arm maze (VRAM).

5.4.3. Interaction Techniques

User interaction with VEs and virtual scenarios might involve several methodological modalities. It could consist of playing serious games or performing different tasks or activities (e.g. IADL). Here, we refer to “tasks” and “activities” in reference to VR systems for ADRD. The term “task” specifically means a particular action that is intended, designed, and established to improve a specific cognitive function, while “activities” involve performing high-level sustained cognitive actions and processes such as: eating, bathing, dressing, shopping, etc. Furthermore, the term “game” refers to activities that are defined by rules and any type of user engagement. Most current VR systems for AD patients that focus on assessment and diagnosis are based on the performance of a task, such as navigation tasks, memorization tasks, etc. Moreover, current VR systems for assessment and diagnosis of ADRD are based on performing tasks, such as navigation or memorization. Furthermore, VR systems for cognitive training concentrate on performing activities that are related to IADL, such as: cooking, driving, shopping, etc. The use of a familiar image-based VE can stimulate recollections of autobiographical memory in healthy elderly subjects, as was

recently demonstrated (Benoit et al., 2015). The fact that episodic autobiographical memory is impaired in early stages of AD (Seidl, Lueken, Thomann, Geider, & Schorder, 2011), suggests that using such type of VR systems may be helpful for reminiscence rehabilitation of AD patients. **¡Error! No se encuentra el origen de la referencia.** classifies VR systems in terms of the methodology used for user interaction.

Recent progress in augmented reality (AR) indicates that this technology may soon become another useful ICT tool for ADRD. This form of mixed reality enhances a non-synthetic real environment by superimposing some synthetic elements into the users' perception of that reality (Baus & Bouchard, 2014). In contrast to VR systems users, who are exposed to simulated VEs (immersive or not), users of AR applications face a real physical location, upon which AR systems introduce additional virtual elements. Some AR applications have been developed in recent years for medically related purposes, such as phobia therapy (Botella et al., 2005; Wrzesien et al., 2014), and for assessment and treatment of psychological disorders (Chicchi Giglioli et al., 2015). A few researchers have conducted appraisals of AR applications for cognitive training and rehabilitation of ADRD patients (Chang, Liu, Kang, Kao, & Chang, 2016; Kirner & Kirner, 2011; Liang, 2015; Quintana & Favela, 2013). Some examples are GenVirtual (Correa, de Assis, Nascimento, Ficheman, & Lopes, 2007), BuildAR (Al-khafaji, Al-shaher, Al-khafaji, & Asmail, 2013), and ARCube (Boletsis & McCallum, 2014).

VR Technology application and/or reference	Participants/Users	Focus Feature	Intended purpose	Interaction technique used					
				Methodology type			Immersion type		
				tasks	games	IADL	Full	Semi	Non
Kalová et al., 2005	11 early-AD; 27 subjective problems with memory and concentration; 10 healthy controls.	Sequential ordering of places, Allothetic orientation, Spatial Navigation, Non-verbal Episodic memory.	Assessment and Diagnosis	X				X	X
Burgess et al., 2006	1 early-AD with topographical disorientation; 4 healthy controls.	Allocentric spatial memory. Topographical disorientation.		X					X
Hort et al., 2007	21 probable AD; 11 amnesic MCI single domain; 18 amnesic MCI multiple domain; 7 non-amnesic MCI; 8 subjective memory complaints; 26 healthy controls.	Spatial memory. Spatial navigation: allocentric and egocentric navigation.		X				X	
Lange et al., 2007	30 Mild Dementia Alzheimer's type; 30 healthy controls.	Visuospatial and wayfinding orientation.		X					X
Cushman et al., 2008	12 MCI; 14 early-AD; 35 young normal controls; 26 older normal controls.	Navigational performance.		X					X
Van Schaik et al., 2008	30 Mild to moderate dementia.	Evaluation of outdoor environments.				X		X	
Zakzanis et al., 2009	8 healthy young adults; 7 older adults with psychiatric or neurological disorders (2 with probable AD)	Spatial navigation. Spatial memory.		X				X	
J Laczó et al., 2010; Jan Laczó et al., 2009, 2010, 2011, 2012	Amnesic and non-amnesic MCI.	Spatial navigation. Hippocampal and non-hippocampal memory impairment.							X
Optale et al., 2010	36 elderly with presence of memory deficits (Verbal Story Recall Test)	Improve memory functions.		X				X	
Weniger et al., 2011	29 amnesic MCI; 29 healthy controls.	Egocentric and allocentric memory.		X					X
Bellassen et al., 2012	16 mild AD; 11 frontotemporal lobar degeneration; 24 normal aging.	Spatiotemporal navigation. Temporal order memory.		X					X
Nedelska et al., 2012	23 amnesic MCI; 19 mild and moderate AD; 14 healthy controls.	Allocentric spatial navigation.		X					X

Table 5.1a - Recent and Current VR applications for ADRD, classified according to the kind of intended purpose and the type of methodological technique used for interaction.

Hofmann et al., 2003	9 with AD; 9 with major depressive episode; 10 healthy controls.	Psychomotor slowing, strategic and critical thinking, cognitive flexibility, problem solving, spatial orientation, delayed recall, long-term memory.	X				X		X
J. Lee et al., 2003 Cognimat Buss, 2009	5 subjects with Traumatic Brain Injury (TBI)	Assess and train cognitive functions involved in basic ADL.	X				X	X	
VIRCOG	6-8 early AD; 4 healthy controls.	Train spatial orientation and working memory.	X				X		X
Lozano et al., 2009	3 patients with neuropsychological disorders.	Improve ADL functioning.	X				X		X
PREVIRNEC Tost et al., 2009	Patients with neuropsychological disorders.	ADL training.	X						X
eGaming Bartolomé, Zapirain, & Zorrilla, 2012	Patients with neurodegenerative disorders.	Cognitive and memory functions		X					X
NeuroRacer Anguera et al., 2013	Healthy young and older adults.	Enhances cognitive control.	X						X
BrightArm Burdea et al., 2013	3 with dementia.	Cognitive rehabilitation of advanced dementia		X					X
IVIRAGE Chapoulie & Guerchouche, 2014	13 healthy elderly adults.	Reminiscence Therapy.	X					X	
FamIBVE Benoit et al., 2015	18 healthy volunteers presenting memory complaints (MMSE score higher than 27);	Reminiscence therapy.	X					X	
Foloppe, Richard, Yamaguchi, Etcharry-Bouyx, & Allain, 2015	79-year-old woman with probable AD.	Support rehabilitation of IADLs.	X				X		X
Manera et al., 2016	28 participants with MCI and 29 participants with dementia (15 AD; 10 mixed dementia; 1 vascular dementia; 2 primary progressive aphasia(PPA); 1 organic brain syndrome)	Train selective and sustained attention	X					X	
O'Connor, Arizmendi, & Kaszniak 2014	7 dementia caregivers.	Online support group.		X					X

Table 5.1c - Recent and Current VR applications for ADRD, classified according to the kind of intended purpose and the type of methodological technique used for interaction.

5.5. FINAL CONSIDERATIONS

This chapter has presented a glimpse at VR-based interventions intended for cognitive diagnostic assessment and training in MCI and ADRD. This account has presented, without pretending to be exhaustive, representative state of the art examples of the most significant types of VR-based cognitive interventions currently available, which we have classified into specific categories to aid in their systematic examination. Our analysis reveals that most of these VR applications still use simple non-immersive or semi-immersive VR scenarios. Therefore, we must conclude that today most VR-based cognitive interventions for ADRD do not yet include VEs with sufficient immersion or interaction capacity to provide the level of “presence” that is desired for cognitive interventions.

Because of the obvious interest in developing personalized ICT-based healthcare applications (Personalized Medicine Coalition, 2014), and the considerable recent advances in the fields of VR and other 3D technologies, as well as in wearable sensors, there is a general urge to continue further development of existing and new medical VR-based applications in general. In the case of cognitive impairment, the improvements and novel developments should translate into the availability of better VR-based applications for ADRD, certainly with more immersive and interactive VEs, based on the latest innovative technologies available (e.g. new HMDs, 3D smart televisions, etc.). The incorporation of emerging video display and interactive technologies will undoubtedly enable innovative designs and implementations of much more effective and versatile supportive VR applications for cognitive diagnosis and training of ADRD patients.

We propose that future developments of VR cognitive assessment and training applications for MCI and AD should prioritize the specificity of the particular needs

of the patients and their symptoms' evolution. VR platform designs must be able to incorporate emerging know-how and techniques, not only to better fulfil the intended specific purposes of VR applications for ADRD, but also to equip those future applications with adequate capacity to supply assistive support to clinicians and caregivers, to significantly contribute to the improvement of the QoL of the patients and their families. Advances in this field should also contemplate providing easy transfer of the applications in a simple and affordable way into in-home and nursing home environments.

Furthermore, a vital feature that will make an important impact on the usefulness of VR interventions for ADRD is the capacity to timely gather and transmit relevant information (Garcia-Betances et al., 2014). Such information must consist, not only of ongoing patient performance data, but also of pertinent psychophysiological data, such as heart rate variability, respiration, electrocardiogram (ECG), electroencephalogram (EEG), etc., and any other multimodal information useful for affective (emotional) state recognition (García-Betances, Fico, Salvi, Ottaviano, & Arredondo, 2015) and cognitive stress detection (McDuff, Gontarek, & Picard, 2014). That data gathering feature must also include immediately accessible real-time feedback, to enable computer artificial intelligence (AI) and specialist controlled intervention during the course of the session. Collected data will provide valuable up-to-date information about the patient's performance evolution, adherence to training and rehabilitation routines, as well as about synchronous physiological reactions of the patient. This feedback capacity is a very valuable tool for implementing closed-loop VR-based interventions, and also is a source of reliable data to build systematic and robust knowledge bases that are indispensable for advancing analysis, research and development in this important area of human cognitive health.

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CHAPTER 6

COMPUTERIZED NEUROCOGNITIVE INTERVENTIONS AND THE BRAIN TRAINING CONTROVERSY

The term “neurotechnology” is often used to collectively refer to the various technologies normally utilized within the field of neuroscience. Modern neurotechnology encompasses several types of tools and applications intended for both neurological sensing and intervention purposes. Among the sensing kind stand out such direct neuromonitoring tools as electroencephalography (EEG), used for measuring central nervous system electrical activity and to generate neurofeedback signals (Sitaram et al., 2017). Other more sophisticated brain monitoring tools that can be used for Computer Aided Diagnosis (CAD) systems (Ortiz, Munilla, Gorriz, & Ramirez, 2016), include advanced imaging and mapping technologies, such as radioactive isotope-based Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT), and functional Magnetic Resonance Imaging (fMRI) (Cohen et al., 2017).

On the intervention side of neurotechnology there are several tools intended to enhance or suppress a certain neurological activity. Important examples include invasive procedures, some of which may be grouped into what, according to the International Neuromodulation Society definition (<http://www.neuromodulation.com/neuromodulation-defined>), is generically known as neuromodulation. Invasive therapies, such as deep brain stimulation (DBS) (Ponce et al., 2016), are typically used to treat serious disorders associated with chronic neural diseases, such as Parkinson’s disease (Shukla & Okun, 2016).

Other stimulation-type neurotechnological interventions considered only minimally invasive include: Focused Ultrasound (FUS) (Miller & O’Callaghan,

2017), transcranial Direct Current Stimulation (tDCS) (McKinley, McIntire, Nelson, Nelson, & Goodyear, 2017), or transcranial Magnetic Stimulation (tMS) (Nguyen et al., 2017). They can be used as stand-alone interventions, or in conjunction with electric neurofeedback to induce some neuroplastic effect at specific brain locations, with the aim of modulating particular brain functions (Sitaram et al., 2017).

In addition to the above mentioned types of direct more or less invasive neurotechnological intervention tools, there exist other indirect-type non-invasive neurotechnological tools and applications that are based on ICTs, that operate through various types of Human-Computer-Interface (HCI) platforms (R. L. Kane & Parsons, 2017). These non-invasive indirect ICT-based interventions are also intended to produce an enhancing or suppressive effect on some brain function. The most important type is commonly known as neurocognitive training (see for example Sharpbrains²⁴), or simply *cognitive training* (CT).

This chapter presents an analytic narrative that examines the use of advanced ICT-based tools for effectively applying non-pharmacological non-invasive cognitive interventions in a current context. Such cognitive interventions are being explored as a means to assess, maintain or improve cognitive functions, or at least to mitigate the behavioural symptoms, of people affected by MCI and ADRD in general (Alzheimer's Association, 2017), and perhaps to some other age-related cognitive impairment-bearing illnesses.

6.1. COGNITIVE TRAINING

Cognitive training (CT) is based on the practice of certain guided mental exercises. Its purpose is to aid in preserving or improving specific cognitive abilities or functions of individuals, such as attention, memory, self-control, decision making,

²⁴ <http://sharpbrains.com/pervasive-neurotechnology>

etc. Hopefully, the improvement will extend to other related but not specifically trained cognitive tasks (far transfer). Many different forms of CT have been, and continue to be, proposed for use by people of all ages and health conditions. Such proliferation is turning these interventions into potentially ubiquitous popular applications. CT is also commonly referred to as either *Brain Training* (BT) or *Mind Training* (MT) in popular literature, newspaper articles, self-help books and commercial products advertisements (Simons et al., 2016).

Various CT interventions are directly aimed at the elderly population. An important portion of them are those specifically developed for people who are affected by some kind of age-related mental impairment, including MCI and ADRD (Magaro, Brotter, & Jalees, 2015; Mahncke, Bronstone, & Merzenich, 2006). There are encouraging results concerning the effects of CT on both healthy and ADRD elderly people. CT interventions for the aging population are widely viewed as potentially effective and relatively inexpensive means of non-pharmacologic therapy (Alzheimer's Association, 2017), that could be capable of improving, or at least preserving, cognition and memory, and possibly sensory and motor functions as well. CT can be useful as part of, or to complement, more comprehensive rehabilitation services, within a goal-oriented re-enablement care strategy approach (Mishra & Barratt, 2016). Such strategies are meant to facilitate people with age-related cognitive impairment to maintain or enhance meaningful functioning, engagement, and participation in everyday life activities with their families and communities (Clare, 2017).

The chief underlying principles upon which all CT paradigms are based evolved from the concept of functional or structural neuroplasticity (Draganski et al., 2004; Guidolin, Marcoli, Maura, & Agnati, 2017; Lindenberger, Wenger, & Lovden, 2017; Román et al., 2017). The neuroplasticity concept is called upon to justify CT

through the widely extended hypothesis that cognitive abilities, akin to physical fitness, can be maintained or improved by the practice of exercise; which in this case means by properly exercising the brain (Mahncke et al., 2006; Shah, Weinborn, Verdile, Sohrabi, & Martins, 2017). Furthermore, this idea is vindicated in the case of the elderly population on the basis of the widely held view that the potential for neuroplasticity continues into old age (Leung et al., 2015).

Modern neurotechnological cognitive interventions are fundamentally the result of the convergence of ICT and mental health. Most CT training nowadays entail the engagement of individuals (normal or patients) through the use of certain platforms in the practice of computer-generated mentally demanding exercises, such as mazes, geometric and mathematical challenges, and many other kinds of so-called serious video games (Anguera et al., 2013; Wang, 2016). Accordingly, this type of CT interventions is frequently referred to as *Computerized Cognitive Training* (CCT). Conceptually, CCT could be thought of as belonging to a boarder class of intelligent computer-based assistive applications, of which the rapidly emerging virtual intelligent assistant gadgets and applications are also part, which have the ability to communicate information through data networks, and are referred as a whole as Intelligent Assistive Technologies (IATs), of course including those specifically aimed at dementia care (Ienca et al., 2017).

CCT is nowadays viewed by most as the preferred and most effective type of tool to use for non-pharmacologic cognitive interventions (Alzheimer's Association, 2017), especially those intended to help preserve cognitive function, or delay the onset of age-related cognitive decline symptoms in people affected by the MCI early stages of ADRD (Alzheimer's Association, 2017). According to a study (García-Casal et al., 2016) of efficacy of CCT interventions, they may be roughly classified into four

categories according to their intended purpose: recreation, rehabilitation, stimulation, and training.

While CCT continues to be investigated and developed, it is also being recommended and adopted as an effective intervention for the elderly population in general. An exceptionally illustrative example of the current widespread application of CCT is a cognitive training program aimed at older people with MCI, that is being massively implemented in Thailand, within a framework based on the concept of living in healthy cities (Chaikham, Putthinoi, Lersilp, Bunpun, & Chakpitak, 2016).

Synergic application of multicomponent neurotechnological intervention of different modalities seems to be a very promising approach for enhancing effectiveness. A good example is a minimally invasive direct intervention, that uses tMS combined with a non-invasive indirect CCT intervention, to improve cognitive performance, locomotor activity, apathy, ease caregiver burden and reduce dependence of patients with ADRD (Nguyen et al., 2017).

Similarly, the combination of neurocognitive-type interventions with non-cognitive type interventions, such as physical exercise, diet, life style, etc., allows to configure simultaneous multi-domain strategies for enhanced effectiveness (Darviri et al., 2016; Shah & Martins, 2017). A representative example of the effectiveness of multi-domain interventions is a recent randomized trial study, called “The Brain Train Study,” of combined cognitive and physical training interventions in aged MCI subjects (Maffei et al., 2017) that provides credible proof of the effectiveness of this type of combined interventions for improving the cognitive status and other indicators of brain health in MCI subjects.

6.2. COMMERCIAL BRAIN TRAINING PRODUCTS

Coinciding with the presently rising scientific attention and renewed research interest in CCT development, there is also a growing popular awareness of brain training applications available in the open market. People in general seem to hold optimistic views and have enthusiastic expectations about brain training. This perception is apparently rooted on some tacit belief that cognitive function can be improved by training, paralleling the widespread notions that most people have about learning in general. Although such convictions have been found not to be universally uniform, but to depend on factors such as age and level of awareness (Rabipour & Davidson, 2015).

Available commercial brain training products come in different presentations, usually in the form of stand-alone applications, or as services delivered through the Internet. Most are being offered as CCT programs capable of boosting attention, processing speed, memory and other cognitive skills (Fitzgerald, 2017). Consumer CCT applications provide mind challenging interactive exercises in the form of various types of cognitive activities, such as puzzles and mazes, as well as in the form of serious games (Anguera et al., 2013; Wang, 2016). The expansion of pervasive and ubiquitous computing, driven by an ever growing availability of all kinds of personal ICT devices, such as tablets and smart mobile phones, is a strong driving force and enabling factor for the current quick proliferation of brain training applications. indicates that There is a high level of popular interest in those CCT consumer applications that are smartphone-based (apps), especially on the part of the younger population, as confirmed by a recent Internet-based survey about use, experience, and perception among people residing in the USA (Torous, Staples, Fenstermacher, Dean, & Keshavan, 2016).

A considerable business sector dedicated to CCT products has been growing over the years, maturing into what today may be referred to as the “brain-training industry.” Companies in this market sector sell their products to healthcare professionals, educators, and the general public. Many CCT commercial applications that may be accessed through a web page, played in a PC, tablet or smartphone, have been developed in different parts of the world. Some representative examples of such commercial products are listed in Table 6.1.

Name	Company	Prominent features (or alleged functions)	Web Portal (http://)
Cogmed Working Memory Training	Pearson Education, Inc., Stockholm, Sweden	For attention problems caused by poor working memory	www.cogmed.com
CogniFit	CogniFit Ltd., New York, NY, USA	Neuropsychological assessments and cognitive stimulation programs	www.cognifit.com
BrainHQ	Posit Science Corp., San Francisco, CA, USA	Online exercises and assessments for attention, brain speed, memory, people skills, navigation, and “intelligence”	www.brainhq.com/
MyHAPPYneuron	HAPPYneuron, Science Brain Training Groupe, France	Personalized and supervised. For memory, attention, language, executive functions, and visual and spatial skills.	www.happy-neuron.com/brain-games
Professional Brain Trainer	Brainer S.R.L., Torino, Italy	Web-based platform for cognitive rehabilitation with over 70 exercises related to different neurocognitive domains	www.brainer.it/caratteristiche/
Fit Brains	Rosetta Stone Ltd., Canada	Memory, attention, speed, and emotional intelligence brain game exercises while having fun.	www.fitbrains.com
Lumosity	Lumos Labs., San Francisco, CA, USA	Cognitive fitness online tool (web and mobile) with numerous training exercises for improving speed of processing, short-term memory, working memory, problem solving, and fluid reasoning.	www.lumosity.com
Brain Age Games	Nintendo’s Brain Age Games, Japan	Quick mental activities to help keep mind in shape: solving simple math problems, counting people going in and out of a house simultaneously, drawing pictures on touch screen, reading classic literature out loud, Sudoku, etc.	www.nintendo.com/games/detail/brain-age-train-your-brain-in-minutes-a-day-wii-u

Table 6.1 – Some examples of typical current commercial brain training products.

The nature of the statements, allegations, and outright claims publicized by different companies is very diverse. Claims are usually said to be underwritten, not only by various kinds of evidence, but also by their creators' professional reputation. For example, Cogmed's developer Pearson Education, Inc. (see Table 6.1) identifies its founders as neuroscientists at the Karolinska Institute in Stockholm and portrays itself as a leader in the field of CCT. The company publicizes several allegations about the effectiveness of their product regarding working memory and lasting improvements in attention. In this case, the claims are comprehensively described in an online document, written on this company's behalf and based on previously published scientific articles (Söderqvist & Nutley, 2017).

Another example of the type of publicity that resorts to the developers' reputation is that from Posit Science Corporation. Their commercial product BrainHQ (see Table 6.1) is explicitly publicized as having been designed by an international team of neuroscientists led by a renowned researcher, described as a member of the National Academy of Sciences, co-inventor of the cochlear implant, and Kavli Prize laureate. The publicity also mentions that more than a hundred published scientific papers, conducted by scientists at respected universities, attest to the benefits of their product.

Similarly, the makers of CogniFit (see Table 6.1), not only publicise their product as being clinically proven, but also assert that it is recognised by the scientific community. To support that claim they provide a list of published scientific articles where CogniFit²⁵ is said to have been reviewed and validated.

One of the best known commercial brain training products is Luminosity, by Lumos Labs, Inc. (see Table 6.1). Luminosity's claims are also ostensibly backed by

²⁵ <https://www.cognifit.com/neuroscience>

scientific evidence. For example, a trial study, funded by this company, asserts that comprehensive training with this product resulted in significantly improvements in cognitive skills compared to the control group, and observed evidence of transfer effectiveness to other untrained measures of cognitive performance (Hardy et al., 2015).

Because of the many CCT paradigms that are possible, and the various promising ICT-based supporting methods available for their delivery, utmost caution must be exercised at all times to preserve the patient's rights to personal safety and health. Therefore, it is essential to ensure that patients are subjected only to totally proven and worthwhile procedures (Gooding et al., 2016). In that sense, it is of paramount importance to scrupulously establish the extent of any potential beneficial effects that may be derived from the use of any method, instrument or platform that is eventually used either by professional clinical practitioners or by the general public.

6.3. THE BRAIN TRAINING DEBATE

Regardless of the more or less substantiated evidence of the effectiveness of commercial CCT products, certain claims made by a few companies that market CCT products at times might have been exaggerated, overstated or have misrepresented their products in ways that could have misled customers. Claims of that kind, or rather, the way how they were presented, have been harshly questioned by consumer advocates (Yong, 2016). In 2016 the US Federal Trade Commission (FTC) of the US Department of Commerce indicted some commercial companies for supposedly making insufficiently substantiated claims in their publicity. In one notorious case, where the courts found defendants responsible of misleading customers, they were

ordered to refrain from making such claims in the future, unless they could provide scientifically solid evidence to back up their claims²⁶.

From then on, several external interests have been vigorously entering the already complex academic debate about cognitive training. The new interests are no longer only those normally associated with legitimate research funding's competitive procurement, but some are also directly related to commercial consumer market profits, as most the world's pharmacological companies normally are. The legal actions undertaken by the US FTC against some commercial brain training companies, although probably warranted, have contributed to heat up the debate, by bringing the issue of brain training effectiveness out of the realm of purely scientific research rigor onto a stage of mass media exposure and public opinion controversy.

Notwithstanding such legal mishaps, supporting evidence of the effectiveness of commercial CCT's continues to emerge. A recent systematic review study (Shah et al., 2017) involving seven representative commercially available CCT programs for cognitive decline indicates that there is clinically significant evidence that supports the notion that some commercially available CCT products can indeed help promote healthy brain aging. In another CCT randomized controlled study (Cavallo, Hunter, van der Hiele, & Angilletta, 2016), conducted using the Brainer platform (see Table 6.1) with a large group of patients affected by early-stage AD, it was shown that significant performance improvements are possible at individual and group levels in the domains of memory, language and executive function. Furthermore, the fact that those improvements remained stable after six months, indicates that intense CCT,

²⁶ FTC vs. LUMOS Labs, Inc., 2016, San Francisco Division of the US District Court for the Northern District of California, Complaint for Permanent Injunction and Other Equitable Relief, The FTC vs. LUMOS Labs, Inc., Case 3:16-cv-00001 Document 1, Filed 1/4/16; <https://www.ftc.gov/system/files/documents/cases/160105lumoslabscompt.pdf>

when specifically designed for each patient's needs, as was done in this study, can be a feasible and effective therapy for early-stage AD.

Still, a significant number of reputed researchers continue to question the scientific soundness of certain claims made about brain training's effectiveness for maintaining, restoring or improving cognitive functions (Fitzgerald, 2017). The fact that sometimes claims have been presented within embellished statements intended for commercial promotion has contributed to disfigure the discussion. However, claims are often truly based on scientifically valid research conclusions and opinions of other equally qualified researchers, who advocate the use of this type of cognitive training interventions. Thus, a pungent controversy has evolved between advocates and sceptics, at times not exempt of strong bias connotations (van Heugten, Ponds, & Kessels, 2016).

At the same time, it is also undeniable that short- and long-term benefits of brain training products had been questioned for quite some time (Jaeggi, Buschkuhl, Jonides, & Shah, 2011). Scientists from around the world have expressed doubts about the effectiveness of brain training in general. The Max Planck Institute for Human Development together with the Stanford Centre on Longevity, in a far reaching attempt to clarify the issue, gathered in 2014 a number of leading cognitive psychologists and neuroscientists so that they could share their views about commercial brain games. The result was a consensus document about the Brain Training Industry (Allaire et al., 2014). Their concluding opinion maintained that claims that were being alleged at the time in commercial advertisements of brain games were often overstated and occasionally deceiving. Two years later, another group of seven psychologists reviewed and analysed published research that had been used to support some commercial products allegations (Yong, 2016). They reportedly

found that the evidence supporting existing commercial claims was what they characterized as “weak.”

Unfortunately, the legitimate questions raised by different scientists in this debate have been simplistically bundled together in many public opinion scenarios, and have ended up being perceived as doubtful, as has been summarized by the question: Does the so-called ‘brain training’ programs work or not?

However, the present situation is far from really being that simple or pessimistic. It is important to remember and emphasise that most, if not all, of the review and meta-analysis studies that to date have not concluded that cognitive training is undoubtedly effective, place the blame for not reaching a positive conclusion on the weakness of the reported evidence of effectiveness. Some studies even express disappointment that the present evidence is not stronger (Simons et al., 2016).

Another important question to consider is the issue of ‘far transfer.’ There is still insufficient evidence to categorically affirm that CCT can produce significant long-term change in the execution of cognitive tasks under real-world situations, or under conditions different from those tasks that were trained by repeated exercise (McCabe, Redick, & Engle, 2016). However, studies on working memory (WM) training have noted gains within the WM domain, although without clear evidence yet of broad generalized far transfer and maintenance effects to other cognitive domains (Vermeij, Claassen, Dautzenberg, & Kessels, 2016). Nevertheless, the still insufficient evidence of successful far transfer in published studies could well be mostly due to common methodological deficiencies, such as small sample sizes (Button et al., 2013), absence of passive control groups, improper measures, as well as other significant procedural shortcomings, as suggested by McCabe, Redick, & Engle (2016). On the other hand, the use of effective VR-based technology for cognitive

training may be changing already the perception of the “far transfer” issue. In fact, results from a very recent ‘development-of-concept’ trial, carried out to assess the efficacy of a novel VR-based training protocol for enhancing the spatial representations ‘mental frame syncing’ of subjects with AD (Serino et al., 2017), show significant improvements in long-term spatial memory after VR-based training. Such encouraging results provide clear evidence that transference from the originally trained-for abilities to more general aspects of spatial cognition is indeed possible with adequately designed VR-based training interventions.

Notwithstanding all the potential and actual deficiencies of the presently available evidence about CCT’s effectiveness, it is essential to insist on the fact that, for the most part, none of the reservations that have been brought up by sceptics arise from solid disproving counter-evidence that would demonstrate that cognitive training does not work, or cannot eventually work. Rather, as we have already explained, the core of this still unresolved controversy rests solely upon the alleged absence of sufficient, bona fide, well-substantiated and rigorous scientific evidence that can prove beyond any doubt that CCT can be an effective neurocognitive intervention tool. In short, the potential effectiveness of CCT is yet to be unquestionably proven, but this is so because the scientific evidence produced up to now may be considered to still be weak mostly because of methodological shortcomings.

Other factors that further complicate this debate include the misgivings expressed by some sceptics and critics about the possible influence of commercial business interests that fund or sponsor research, whose findings are then reported in articles published in specialized journals. Similarly, there are some worries about possible publication bias and selective reporting practices (Simons et al., 2016), that could be inadvertently contaminating some of the meta-analyses. The possible presence of placebo effects could also alter the results of cognitive intervention trials,

as apparently happened, because of enticing recruiting advertising, in a cognitive training study (Foroughi, Monfort, Paczynski, McKnight, & Greenwood, 2016). Therefore, assessments of future trial cases must include measures to prevent or correct such possible bias and placebo effects.

As we have mentioned already, sceptics' allegations are being tenaciously disputed by many qualified advocates of cognitive training. Consequent with their convictions, numerous proponents continue to carry out further and more extensive quality testing to corroborate that cognitive training can indeed work. Meanwhile the ongoing debate continues to cause a negative impact on the evolution of CCT paradigms in general. Particularly troublesome is the detrimental influence that excessive public exposure of the debate can have on potential support of research and development activities needed to bolster CCT.

The present reality of this not yet fully resolved debate is that the available published meta-analyses on the subject provide promising but still insufficient evidence that leads to different and sometimes conflicting conclusions (Makin, 2016). Given such a state of affairs, it seems reasonable to ask ourselves a fundamental question regarding the immediate future of R&D activities in the field of CCT interventions in general, and in our case, more specifically those aimed at MCI, ADRD and other neurodegenerative age-related cognitive impairments. The new question to be answered nowadays is as follows: Given the context of the ongoing brain training debate, should R&D of CCT interventions continue to be pursued? Or alternatively: Should such activities be promoted, supported and funded?

Considering the abundance of promising results that have been already reported, bearing in mind that most of the work done so far on the use of VR technologies for ADRD intervention have involved the use of unsophisticated ICTs and non-immersive VR-based solutions, and taking into account the fast progress of

innovative highly immersive VR technologies, our answer to this essential question is certainly affirmative. This conviction is by no means in conflict with acknowledging that the effectiveness of many of today's commercially available CCT products has yet to be rigorously proven. But we reject as baseless, as most experts do, the very notion that all CCT interventions are ineffective, or that human cognitive functions in general cannot be trained. To be coherent with this affirmation, we will substantiate our viewpoint in the following sections, and will explain the reasons why R&D activities should continue to be decidedly pursued and supported to improve the effectiveness of CCT interventions in general, and those for MCI and ADRD in particular,.

6.4. THE POTENTIAL OF VR-BASED COGNITIVE TRAINING

Early studies investigated the potential of using non-immersive VR environments for CCT applications. A good example of such early technology is a VR system used to improve the functional cooking autonomy of AD patients (Foloppe, Richard, Yamaguchi, Etcharry-Bouyx, & Allain, 2015). Although it was a single case study, it was enough to demonstrate that even such non-immersive VR can be useful to improve a patient's functional ability. A more advanced type of interaction for VR-based CCT is the modern HMD. As we have already mentioned, advanced VR technologies offer the possibility of simulating immersive and interactive 3D life-like virtual scenarios to create in the user what we have called a sensation of 'presence' or 'being there.' Fully 3D immersive VR-based interactive platforms allow to perform tests and exercises within dynamically adaptive real life-like environments that can be adjusted according to various diagnostic and therapeutic requirements, and even customised to the patient's own personal needs. Such type of innovative instruments are constantly being improved, and are already been considered for advanced

neuropsychological assessment and for therapy for phobias, stress, anxiety, exercise, memory problems, etc. (García-Betances, Jiménez-Mixco, Arredondo, & Cabrera-Umpiérrez, 2015; Garcia, Kartolo, & Méthot-Curtis, 2012; Riva, 2005; Rizzo, Buckwalter, & van der Zaag, 2000).

Future CCT developed to meet the needs of the elderly population will surely benefit from a more intensive use of the value added by the use of innovative VR-based platforms designed specifically to better address the particular requirements of cognitive impairment mitigation. Such tools can be of great assistance, within a comprehensive cognitive rehabilitation scenario, to medical personnel, health care workers, and caregivers in general, for enhancing the quality of life of elderly people with MCI and ADRD. To that end, we have suggested criteria and strategies for effective design and development of VR tools for MCI (García-Betances, Jiménez-Mixco, et al., 2015). Such tools, once equipped with adequate protocols and procedures, and making use of the most advanced immersive and interactive capabilities of emerging and next-generation VR technology, represent the future of CCT cognitive interventions, as we suggested in a brief review of VR technology to be used in patents with ADRD (García-Betances, Arredondo Waldmeyer, Fico, & Cabrera-Umpiérrez, 2015).

Cognitive exercises based on VR-based intervention platforms happen to be well suited tools to assess and stimulate functional abilities associated with cognitive and motor activities of daily life in domains such as spatial memory, executive functions and cognitive flexibility in patients with MCI or early ADRD. As explained before, VR technology opens up the possibility of dynamically adjusting and self-pacing the cognitive intervention content, according to the changing requirements of the ongoing diagnostic or therapeutic experience, as well as responding to the individual needs of patients during the course of the intervention. VR also can serve

to significantly enhance patient engagement through the use of enticing environments and proven motivational techniques, such as reward feedback, that together induce a competitive spirit in the participants, while maintaining an attractive sense of wellbeing. Emerging 3D fully immersive stereovision features of today's advanced VEs, possibly equipped with AR-like enhanced scenarios, as well as with other imbedded interactive multi-sensorial next generation capabilities, will play an essential role in generating realistic stimuli within the VR platform to provide vivid egocentric point-of-view sensations that will amplify and expand the desired effect of the intervention.

The validity of VR systems with some of these characteristics, was recently assessed specifically for motor training of balance and postural control tasks in groups of aged healthy and MCI subjects (Bourrelier et al., 2016). Other feasibility studies have been also conducted with MCI and dementia patients investigating the use of highly realistic image-based rendered VR. One study (Manera et al., 2016) found that VR-based CCT resulted to be useful to improve adherence of elderly people with cognitive impairment to the training exercise.

On the other hand, simpler semi-immersive VR technology should not be totally discarded as it may still be useful. A recent study uses such VR-based active navigation to improve the visuospatial orientation ability of people with cognitive and physical disabilities (de la Torre-Luque, Valero-Aguayo, & de la Rubia-Cuestas, 2017).

There are currently some efforts to develop more objective performance-based and observational assessments of cognitive and functional capacity deficits to be used as tools to detect early stages of the ADRD (preclinical, pre-MCI, and MCI) (Harvey et al., 2017). The requirements for these assessments clearly favour the use of the latest advanced computerized strategies, such as the quickly evolving VR

technologies, which are the best way known to date to vividly simulate everyday life functional conditions.

It is already well known that VR can provide an effective means for objective and appropriately controlled assessment of episodic memory (Plancher & Piolino, 2017). But VR may be also helpful to assess many more aspects of cognition other than episodic memory. Advanced VR environments could provide the ideal platform for implementing novel tests of metacognition, social cognition, and prospective memory, as has been recently recommended by the Working Group on Cognitive Assessment of Early AD in Clinical Trials of the International Society for Clinical Trials and Methods (ISCTM) (Harvey et al., 2017). VR's inherent dynamic navigation capacity with high levels of immersion and interaction will ease the challenging processes of diagnosing MCI and early ADRD. It is clear today that VR technology represents one of the most promising tools for providing non-pharmacological interventions for dementia (Raggi, Tasca, & Ferri, 2017).

In addition to VR's usefulness for CCT and cognitive assessment interventions, VR environments also can be used as an effective research tools. An example is a recent study that explored the potential of using a HMD-based immersive VR driving simulator to investigate how age affects the driving ability of aging adults (Bennett, Corey, Giudice, & Giudice, 2016). Regarding research, VR will become a vital tool for advancing spatial memory research, much needed to empower the development of potential neurorehabilitation tools for topographical disorientation in AD (Raggi et al., 2017). Additionally, some of the still evolving advanced VR-based tools for assessment interventions will facilitate opening up some yet unexplored avenues for research; for example understanding fundamental neurological mechanisms, such as episodic and other types of memory associated with

cognitive functions (García-Betances, Cabrera-Umpiérrez, Ottaviano, Pastorino, & Arredondo, 2016; Plancher & Piolino, 2017; Raggi et al., 2017).

6.5. DISCUSSION

Most research studies about CT conducted during the last two decades or so clearly suggested that CT could be beneficial for elderly people (Ball et al., 2002) as well as for patients with MCI and dementia (Jean, Bergeron, Thivierge, & Simard, 2010). The Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study of the U.S. National Institutes of Health²⁷ established that the application of cognitive training for memory, reasoning, and speed of processing results in a reduced decline of self-reported independent activities of daily living (IADL), and that training of reasoning and processing speed, but not memory, produced improved cognitive abilities retention for 10 years (Rebok et al., 2014). Although the use of CCT is a promising beneficial non-invasive neurocognitive intervention for older adults, its effectiveness probably declines slightly with age (Motter et al., 2016).

Not all studies conducted on this subject have reported positive results. Some have failed to discover significant evidence after training of the sought for improvement. For example, a recent study of cognitive training trials with 97 healthy older adults aged 65 and over (Goghari & Lawlor-Savage, 2017), could not find any noticeable after-training improvement nor near or far transfer of working memory, planning, reasoning, verbal fluency, cognitive flexibility, creativity and processing speed. But such lack of evidence in this study, and others, does not necessarily mean, as we have already commented, that the used training protocol is ineffective. A very plausible explanation in this case is that the healthy elders that comprised this study's

²⁷ <https://clinicaltrials.gov/ct2/show/NCT00298558>

cohort were before training already at or around their maximum cognitive level for their age, so that no significant improvement should have been expected. Of course, there might have been other instrumental reasons for having failed to observe changes in this case. For instance, that the assessment tools used for comparison were not acute enough to perceive the resulting very small changes. This example, is mentioned only to underscore the importance of precise conceptual definition and methodological rigor when performing meaningful cognitive training trial studies.

In contrast to trials that predictably yield marginally noticeable changes, there are others that in principle should be expected to produce evident changes. That is the case of a study of cognitive training for a large number of older MCI patients with low education level living in Chinese rural areas (Liu et al., 2016). In that case two months of training did produce, as expected, observable beneficial and long-term cognitive changes on attention, language, orientation, visual perception, organization of visual movement, and logical questioning.

Methodological deficiencies unfortunately plague many cognitive training studies. A recent systematic review of cognitive training interventions to improve or stabilize cognition and everyday functioning in patients with AD (Kallio, Ohman, Kautiainen, Hietanen, & Pitkala, 2017) uncovered several types of such shortcomings in many of the studied trials. Most prominent were: inaccurate descriptions of training exercises, inadequate statistical procedures, and incomplete follow-ups. The findings emphasize the need for well-designed RCTs in order to corroborate that cognitive training indeed can become an effective treatment (Button et al., 2013). Additionally, including both active (fake training) and passive (no training) control groups in the design of any RCT study is a vital requirement to be able to accurately analyse resulting evidence. The capital importance of including such control groups was

recently illustrated by the intriguing results reported in a study about CCT use to improve executive functioning after stroke (van de Ven et al., 2017).

In addition to focusing on neuropsychological aspects directly related to cognitive abilities, it would be worthwhile that future studies also consider daily functioning, self-efficacy and QoL aspects, as has been amply suggested (van Heugten et al., 2016). A relevant example of this kind is a study about three cognitive training programs on automobile driving cessation for older adults at-risk for mobility decline due to cognitive impairment (Ross, Freed, Edwards, Philips, & Ball, 2016).

We already mentioned that the integration of motivational strategies into cognitive intervention protocols to stimulate engagement will be of vital importance (Gooding et al., 2016). The introduction of the latest immersive VR technologies into CCT, coupled to realistic multi-sensorial interaction devices and neurophysiological feedback capacities, are perhaps the main aspects that are expected to provide the most impacting improvements that can be made to CCT for MCI.

To be able to produce solid evidence of cognitive training effectiveness, specific measures of objective evaluation must be instrumented. Long-term follow-ups are needed to appraise the retention potential of the intervention effects (García-Casal et al., 2016). As we already mentioned, a crucial desirable aspect of CCT interventions is the ability to transfer the potential effects to other not-trained activity domains (far transfer capacity). Although not yet fully demonstrated, there is sufficient evidence from some experiences to expect that the use of VR in CCT will increase the probability of far transfer to real daily life situations.

There is also evidence that training can yield improvements of sensory perceptual abilities in both young and older people. It has been demonstrated that experience and training result in long-term visual perceptual learning (VPL) (Sasaki & Watanabe, 2017). In that regard, VR might turn out to be the ideal supporting

platform for sensory perceptual training of complex stimuli. Coupled to other analytic neurotechnologies, such as advanced neuroimaging, VR may become helpful for understanding plasticity at the sensory and decision phases in the normal as well as the cognitively impaired human brain. Synergic use of advanced CCT tools, such as VR, together with sophisticated brain monitoring tools, will help in advancing the growing field of model-based cognitive neuroscience (Palmeri, Love, & Turner, 2017). Combined multi-modality interventions will one day facilitate testing model hypotheses about cognitive mechanisms of human perception, learning, remembering, and deciding, within a mathematical psychology framework.

A recent editorial article (van Heugten et al., 2016) stated that brain training studies in general have shown up to now only promising signs of being effective in healthy persons and patients with cognitive deficits. Therefore, it advised to consider those studies only as proof-of-concept evidence that suggest that cognitive improvement may be possible through training. In spite of the mounting optimistic evidence, as of today, it is still unknown how much VR and other advanced computer technologies may be able to slow down the course of age-related degenerative cognitive impairment such as incipient dementia. Much less certain is whether such ICT tools will eventually help to arrest their course, and if so, under what conditions and circumstances. It is therefore evident that if we pretend to ever answer these important questions in an undisputable manner, more and better systematic research is still needed on the subject.

Since most early studies do show promising results, further systematic research is indeed warranted to explain, reproduce and expand the initial results (Allaire et al., 2014). Most researchers agree that the cognitive training field needs more, larger, and methodologically sounder studies, as well as revisiting the pertinent basic science (Makin, 2016). The application of adequate and proven learning

strategies based on existing knowledge about memory phenomena, as suggested by McCabe et al. (2016), will lead to more effective CCT procedures, at least in the important domain of WM. Further research is needed to ascertain the effectiveness of CCT interventions in general, but especially in the categories of cognitive recreation, rehabilitation, stimulation, and training interventions for people with dementia (García-Casal et al., 2016).

Research, development and design activities on advanced forms of CCT, based on emerging ICT such as VR, must be encouraged, together with careful analysis and validation of their effectiveness. Considering the growing promising evidence and a reasonable expectation of the potential benefits, the question to ask in the present context is no longer whether or not CCT works, rather: *What characteristics and conditions are required by advanced CCT platforms, such as VR and other emerging ICTs, to be able to induce significant, transferable and lasting beneficial effects in patients with MCI?*

We have sought to shed some light on the repercussions of the ongoing debate regarding the effectiveness of some of today's consumer-oriented commercial brain training products. In that course, we have drawn attention to one crucial fact: That the most relevant reservations that have been brought up in this debate refer only to alleged lack of sufficient methodologically rigorous scientific evidence to unquestionably support advertised claims of commercial products. The emphasis is placed on the term sufficient. We have argued that the persistence of this debate does not imply by any means that CCT paradigms have been found to be essentially ineffective. Much less that cognitive functions in general have been proved to be untrainable. Quite on the contrary; given the very promising evidence published about CCT, and in view of the good prospects for substantial near-term advances in emerging ICT-based technological tools, such as VR, we strongly advocate the

continued pursuit of further research efforts in the field of CCT. We propose that particular attention be given to developing novel neurocognitive intervention VR-based platforms aimed at mitigating the symptoms of cognitive impairment afflictions. Advanced ICT-based platforms' immersive characteristics and interactive functions are of particular relevance for treating many of the main symptoms of MCI and other neurodegenerative age-related cognitive decline illnesses, especially in the domains of memory, sustained attention, executive ability to make decisions, spatial orientation, and time and visual perception.

There is no doubt that more RCTs of CCT must be carried out in a scientifically rigorous manner, and that their results should be subjected to methodically scrupulous analyses. However, it is also clear that it is not enough to just do better experimental validations of existing neurocognitive training paradigms, most of which are based on antiquated neurotechnological tools. If this promising and potentially important field is to make further progress, it is essential to undertake new CCT platform design initiatives. Better and more resourceful platforms based on advanced ICTs, especially those capable of multi-domain and multi-modality operation, are necessary to support the delivery of the future CCT interventions.

It is also essential that future novel methodologies and strategies be based on a correct knowledge of human brain functionality, as well as on a better understanding of the structural, physiological, functional and neurochemical basis of brain plasticity. Since cognitive training might unequally affect different brain regions and modify the spatial distribution of functionally relevant sub-networks (Taya, Sun, Babiloni, Thakor, & Bezerianos, 2015), monitoring and studying the brain's structural connectome (Guidolin et al., 2017), through image analysis, will supply vital information about cognitive training-induced structural connectivity and plasticity changes within specific sub-networks in the brain (Román et al., 2017). Other

important aspects of interest for CCT could be selective plasticity stabilization, its trained-skill specificity, and the individual differences present among specific domains (Lindenberger et al., 2017). In the long run, the ever growing corpus of knowledge related to neurological functionality and plasticity will undoubtedly benefit from the information to be gathered from the feedback that future CCT interventions will provide.

Regardless of the course of the public brain training debate, CCT tools have already demonstrated their feasibility as a promising neurotechnological therapeutic option for ameliorating cognitive deficit symptoms. Thus, CCT ought to be further explored through emerging ICT to fully reveal and develop its potential capacities, as well as to be able to reliably appraise the real implications of its possible benefits. We have mentioned important factors that need to be considered for improving the significance, rigor, reproducibility and reliability of any future research on this topic. We recall here just three of them: proper selection of samples of broadly and narrowly defined target populations; precise specification of the intervention's possibly multiple active ingredients; and the assessment of the intervention's effectiveness through rigorous patient-centred outcome measurements. The assessment factor should be focused not only on traditional clinical measures of impairment's symptoms reduction, but also on innovative measurement of improvements in daily life functions (Rodakowski & Skidmore, 2017).

Future work should concentrate on the use of emerging advanced forms of ICT-based CCT platforms, especially the latest-generation VR and several other emerging or yet to emerge high tech resources. There are already sufficient reasons to believe that increasing the levels of immersion and interaction of the CCT environments through the use of advanced VR technologies will notably improve the efficacy of the interventions by enhancing their potential to induce larger effects.

Summing up, the question today no longer is whether to use ICT-based neurocognitive intervention, but how to do it. Pursuing further research and development, if conducted within appropriate frameworks, is not only warranted but necessary, and should be decidedly encouraged and supported. Progress in this direction will greatly enhance our ability to preserve older people's cognitive health (Medalia & Erlich, 2017), the single major factor that conditions their personal independence and QoL, as well as that of their relatives and care-keepers. In today's scenario of increasing human life expectancy, longer life-spans must be matched by similarly long 'health-spans' of the aging population (Kaeberlein, Rabinovitch, & Martin, 2015). An essential requirement for promoting healthy aging is safeguarding older people's cognitive health, an urgent task that today represents a challenge with human, societal and economic repercussions.

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CHAPTER 7

METHODOLOGICAL DESIGN FRAMEWORK

There are certain basic considerations that must be adhered to when developing advanced VR technology-based cognitive interventions platforms and applications. Foremost of all is a principle that not for being obvious should go unmentioned. It refers to the need to bear in mind that, as with any technology-assisted healthcare application, the underlying reason for using VR platforms, or any other advanced ICT, to administer neurocognitive interventions, is not and can never be the use of new technology per se. Rather, the motivation should always be providing better interactive and sensory-rich environments that will empower the cognitive intervention experience in order to more effectively express its diagnostic or therapeutic intended potentialities.

Therefore, the design of VR applications for cognitive interventions, in addition to the typical technical challenges common to any VR design in general, confronts other specific challenges. These challenges, that are not necessarily only technical, are peculiar to and arise from the nature of the cognitive intervention application's intended specific purpose and experience modality. Satisfying such particular requirements translates into the need for a “designed-for-the goal” customizable type of design procedure.

This chapter presents and describes a proposed methodological design framework of VR interventions for cognitive disabilities care, specifically for people with ADRD. The definition of the methodological design framework aims to facilitate the optimization of the effectiveness, performance and reliability during device development and design stages of such VR-based advanced technology applications for ADRD, following certain best practice guidelines to obtain more precise, reliable

and easy to compare results (Vos, Marin, Escalona, & Marchetto, 2012). The application of the presently proposed methodological design framework will contribute to: (1) the conceptualization of the study/solution; (2) the modelling of the resources and the system implementation; and (3) the definition of the evaluation approach and how to execute it.

In the following sections we will analyse guidelines and recommendations, assess the strengths and weakness of the applicability of VR-based solutions in cognitive disabilities care, describe a new criterion of well-defined methodologies, and present the methodological design framework concepts and components.

7.1.GUIDELINES AND RECOMMENDATIONS

This section analyses existing design and evaluation guidelines that were conceived during the execution of various studies and/or research projects. We cover general guidelines of ICT design processes, design guidelines specifically for people with cognitive disabilities, as well as evaluation methodologies and good practices for the evaluation of cognitive training programs.

7.1.1. General purpose VR application software design guidelines

There is a large number of information resources readily available online in the Web which provide general design guidance advice to facilitate the technical work of VR applications software developers. Most contain some kind of best practices information that can be very useful to follow by developers of all levels. Although we encourage adherence to such type of guidelines and best practices when designing software for VR-based cognitive applications, it is not the purpose of this thesis to add to an already large and growing body of general purpose VR software design guidance information. However, for the sake of completeness and illustration, we offer below, without pretending to be exhaustive, a short list of some sources that we

believe to be representative examples of general purpose and platform specific resources currently available in the Web.

1. Designing for VR - A Beginners Guide: <https://blog.prototypr.io/designing-for-vr-a-beginners-guide-d2fe3790>
2. An introduction to VR experiences / Best Practices:
https://developer.oculus.com/design/latest/concepts/bp_intro/
<https://developer.oculus.com/design/latest/concepts/book-bp/>
3. VR Design Best Practices: <https://medium.com/@LeapMotion/vr-design-best-practices-bb889c2dc70>
4. Design Practices in Virtual Reality: <https://uxdesign.cc/design-practices-in-virtual-reality-f900f5935826>
5. 7 things to know about designing for virtual and augmented reality:
<https://www.invisionapp.com/blog/designing-for-vr-ar/>
6. Designing for Google Cardboard: <https://www.google.com/design/spec-vr/designing-for-google-cardboard/a-new-dimension.html>
7. VR Design Best Practices for Google's Daydream VR platform:
<https://www.roadtovr.com/vr-design-best-practices-google-vrs-alex-faaborg/>
8. Mozilla A-Frame, for WebVR, used on browser platforms and different types of headsets: <https://aframe.io/docs/0.6.0/introduction/#what-is-a-frame>
<https://mozvr.com/>
9. Daydream VR, for midrange VR in mobile phones only:
<https://vr.google.com/daydream>
10. Unity VR, for high end headsets:
<https://unity3d.com/learn/tutorials/topics/virtual-reality>
11. Unreal developer kit SDK, for high end headsets:
<https://www.unrealengine.com/en-US/what-is-unreal-engine-4>

7.1.2. User-centred design guidelines

Technological progress and market pressure have led to the development of increasingly complex products and systems with numerous functionalities. Different issues, such as: complex interfaces, accessibility issues, comprehension problems, etc., during the design and development of products and systems produce a usability gap that occurs between user's low technological specialization and the high complexity of the product. The challenge is to reduce this usability gap by including end users' characteristics, needs and limitations during the design process. Design interfaces that satisfy both skilled and inexperienced users is also a challenging task (European Telecommunications Standards Institute, 2009).

As ICT solutions increasingly become an indispensable part of the lives of elderly people, as well as those with disabilities in general, it is of paramount importance for researchers and developers of ICT solutions to devise and adopt new design methodologies that devote special attention to these people's particular needs and requirements (Wagner, Hassanein, & Head, 2010a). These people's ICT needs differ considerably from those of a normal or younger user. People's functional impairments derived from disabilities come in a wide variety of manifestations and generally differ broadly from one case to another. The severity of any pre-existing disability likely will increase with age. On the other hand, previously healthy people will certainly develop aging-related functional and cognitive impairments as they approach old age (Microsoft Corporation, 2003; Wagner et al., 2010a). Therefore, researchers, developers and designers nowadays must incorporate new paradigms to their repertoire of service personalization tools, in addition to users' self-customization. These new paradigms gravitate around the perspective of an inclusive and universal design concept to satisfy the needs and requirements of particular groups of users, such as the elderly and people with disabilities (United Nations,

2006; Wagner et al., 2010a). Some of these problems are related to usability issues, such as: functional limitations, behavioural and cognitive limitations, reduced capabilities, etc., which could strongly influence user acceptance (Eberle, Schwarzsinger, & Stry, 2011; LeRouge, Ma, Sneha, & Tolle, 2013a).

Both groups of elderly people and people with disabilities have distinct needs and concerns different from those of general users, because of their cognitive and physical impairments originated by aging or from some disability. These needs and concerns are often ignored during the design and development process of ICT-based applications (LeRouge et al., 2013a). Various studies and developments have been carried out to overcome several of the technological barriers faced by users affected by specific impairments or limitations, by taking into account their particular characteristics and needs (Alm & Nakamura, 2001; Ferreira et al., 2013; Gregor, Newell, & Zajicek, 2002; Newell & Gregor, 1997a).

In order to produce interactive systems with high usability and user acceptance, it is necessary to involve end-users throughout the whole design and development process. One of the most commonly used methods to place the user at the centre of the development process is the User-Centred Design (UCD) approach proposed by Norman's Research Laboratory at the University of California, San Diego (Norman & Draper, 1986).

UCD is a kind of modern Human Computer Interaction (HCI) design methodology that is based on inquires, assumptions, and analysis of users' needs, desires, and limitations during the design process of ICT solutions (LeRouge, Ma, Sneha, & Tolle, 2013b). The principal objective of UCD is to include the user into the design process by way of different user modelling techniques that typify a group of users, such as: feature-based, content-based, case-based, scenario and goal-oriented, knowledge-based, demographic modelling, etc. (Ferreira et al., 2013; Kurschl,

Augstein, Burger, & Pointner, 2014). Despite the potential benefits of UCD methodologies, their use in particular for health technologies has not received much attention (LeRouge et al., 2013b). This is true also in the context of applications for aged patients. Although the technical literature provides little guidance and directives about how to involve older people during the design and development process, some works have already taken into consideration this population segment (Ferreira et al., 2013; LeRouge et al., 2013a).

Users can also be classified specifically into different particular needs and characteristics, and within various environments (Fischer, 2001). A classification of users merely according to their expertise and knowledge (e.g. novel, intermediate, and expert) is not usually enough. Particular issues specifically relevant to the capabilities of elderly users must be taken into consideration during the process of ICT intervention design process (Gregor et al., 2002). The principal aspects that need to be considered more carefully are those related to: physical, sensory, and cognitive abilities; learning capacity; memory problems; environmental factors; and accumulated experience.

In order to distinguish between different user groups by focusing on the user's needs instead of on user's capabilities, the concept of "Persona" was introduced in 2004 into the design process. Within that context, *"Personas are not real people, but they represent them throughout the design process. They are hypothetical archetypes of actual users."* (Cooper, 2004). Working with the "persona" concept throughout the entire design process helps researchers and designers understand and effectively take into account user's needs. This type of conceptual methodology for ICT system design, which is more aware of users' abilities and limitations, has already been utilised by some researchers and developers (Casas et al., 2008; Castillejo, Almeida, & López-de-Ipiña, 2014; Cooper, 2004). Furthermore, combinations of this "persona"

design concept and other user-centred design (UCD) methodologies, such as ‘goal’ and ‘scenario’ modelling, also have been put together. A mixed Persona-Scenario-Goal (PSG) methodology was also suggested as a logical extension of the persona-scenario methodology (Aoyama, 2007).

Methodological processes of UCD are currently evolving towards cognitive support-type implementations (Harte et al., 2014). It is convenient to emphasize the introduction of cognitive user processes into user modelling techniques. The argument is that it should be possible to “*state adaptation methods and techniques in terms of a cognitive aid vocabulary*” (Eberle et al., 2011). The use of cognitive tools and techniques frees the designer and developer from having to make speculative suppositions or dubious estimates about medical conditions and other related issues. Innovative assistive technologies must embrace UCD methodologies and techniques to capture the user’s perspective, and to implicate in their solutions users’ goals, abilities, and needs, as well as the user’s vital context or scenario (Dubey, Gulabani, Mewara, & Trivedi, 2014).

The seven rules for UCD proposed within Norman and Draper’s approach (Norman & Draper, 1986) are:

1. ***Use both knowledge in the world and knowledge in the head:*** it refers to provide clear instructions and user guides about the system, taking into account the user’s knowledge needed to understand the system.
2. ***Simplify the structure of tasks:*** it refers to simplifying the tasks all over the system in order to liberate the user from having to memorize or learn long chains of actions.
3. ***Make things visible: bridge the gulfs of execution and evaluation:*** it refers to the ability to easily understand what functionalities the

different parts of the interface has without the need to provide any additional information.

4. ***Get the mapping right***: it refers to using some standard organization of elements within the graphic visualization.
5. ***Exploit the power of constraints, both natural and artificial***: it refers to providing clear indications of what is possible or not to do during a set of actions.
6. ***Design for error***: it refers to defining, during the design process, a mitigation plan for the possible errors that can occur or can be made by the user.
7. ***When all else fails, standardize***: it refers to following common standards (e.g. industrial, professional, international, etc.) during the design process whenever decisions have to be made arbitrarily.

Since Norman and Draper's UCD approach does not necessarily consider active involvement of the user during the design process, several complementary definitions and sets of principles have come up over the years. Nowadays the most widely adopted approach still is the one originally described by Gould and Lewis (Gould & Lewis, 1985; Sharp, Rogers, & Preece, 2007). This approach defines three main aspects of UCD that should be the basis for the implementation of UCD in design projects. It provides a more comprehensive and simplified framework for their implementation. The three main proposed aspects are:

1. ***Early focus on users and tasks***: understand, observe and study users and the nature of their usual tasks, with the goal in mind of including the user in the design process. Such viewpoint will necessarily lead to considering the user's cognitive, behavioural, anthropomorphic and attitudinal characteristics.

2. ***Empirical measurement***: observe record and analyse the user's performance and reactions, using sketched scenarios or mock-ups (on early stages), and simulations and/or prototypes (on later stages).
3. ***Iterative design***: the design and development process must be iterative, based on users' feedback during user testing. The process comprises iterative cycles of "design, test, measurement, and redesign." The identified problems should be pinpointed and retested to grasp the effect of any improvement.

Gould and Lewis approach (Gould & Lewis, 1985) was translated into an ISO international standard called "ISO 13407:1999 - Human-centred design processes for interactive systems" recently changed and updated to "ISO 9241-210:2010 - Ergonomics of human-system interaction -- Part 210: Human-centred design for interactive systems."

This international standard ISO 9241-210:2010 is currently the basis for many UCD methodologies (International Organization for Standardization, 2010). It defines the UCD as "*an approach to interactive systems development that aims to make systems usable and useful by focusing on the users, their needs and requirements, and by applying human factors/ergonomics, and usability knowledge and techniques.*" According to this standard, the key principles that every human-centred approach should follow, regardless of their characteristics, are:

1. The design should be based upon an explicit understanding of users, tasks and environments;
2. Users should be involved throughout design and development;
3. The design should be driven and refined by user-centred evaluation;
4. The process should be iterative.

The standard also describes four user-centred design activities and their specific outputs, as is shown in Figure 7.1.

Figure 7.1 – User-centred Design activities and outputs for user-centred design

In summary, UCD methodology can be divided into four general phases (Haklay & Nivala, 2010): (1) analysis; (2) design; (3) evaluation; and (4) implementation. Figure 7.2 shows these four phases and its relationships, along with their links with UCD activities and outputs as suggested by the ISO 9241-210:2010 standard (see Figure 7.1). The whole design process is based on iterative cycles that are repeated during the phases of “design, evaluation and implementation” of the UCD approach. Each phase is described below:

- *Analysis*: understand and specify the context of use of the design outcome and ascertain user requirements. The context of use should describe the characteristics of the potential users (user groups), key goals and constraints (user needs and goals), tasks, and organizational, technical and physical environment or context in which the design outcome will be used, as well as the interpretation as requirements of data collected from users.
- *Design*: of the User Interface Concept. The main purpose is to produce design solutions of the intended User Interface based on user requirements. Prototypes and preliminary muck-ups are part of this phase.
- *Evaluation*: evaluate and validate the developed concept with end users, by means of usability criteria (e.g. effectiveness, efficiency, satisfaction, memorability, and/or minimal errors, etc.). The process should go back to the definition of user requirements whenever the results indicate that the user requirements have not been met.
- *Implementation*: of a version of the prototype for evaluation, although it is advisable to create different design alternatives so they can be evaluated side-by-side in some cases.

Figure 7.2 – User-centred Design process

Despite the potential benefits of UCD methodologies, their use has not received too much attention for health technologies in particular (LeRouge et al., 2013b). This is unfortunately also true within the context of applications for aged patients. Although the existing literature provides little guidance or directives about how to involve older people in the development and design process, there are some studies have been carried out taking into account this population segment (Ferreira et al., 2013; LeRouge et al., 2013b).

7.1.3. Classification of Functioning, Disability and Health

ICT applications and services usually were unable to guarantee a comfortable interaction for most types of these users. An official medically-oriented study, produced and published in the 1980's by the WHO, provided some guidance regarding special user abilities and conditions ensuing from aging or disability derived functional impairments. That study proposed a classification that was first known as the International Classification of Impairments, Disabilities, and Handicaps (ICIDH). A new version came out in 2001, called the International Classification of

Functioning, Disability and Health (ICF) was approved by the WHO World Health Assembly (World Health Organization, 1980, 2001). This ICF classification defines and classifies health and other health-related domains. The document includes the concepts of “health” and “disability,” the environmental factors involved, their impact, a classification of every function state associated with health (e.g., diseases, disruptions, injuries, traumas, etc.), and a common framework to allow all conditions to be compared using common metrics. The ICF documentation represents an essential starting reference for researchers, developers and designers to identify user capabilities and conditions that shape the settings of the interaction processes (Castillejo, Almeida, & López-de-Ipiña, 2014; Castillejo, Almeida, López-De-Ipiña, & Chen, 2014).

7.1.4. Gender-based personalization of UCD

When personalizing VR-based cognitive intervention design, it is indispensable to be aware of the pertinent influencing factors that condition each particular patient. The required knowledge starts with the individual patient’s most prominent characteristics and circumstances, such as social and economic status, health condition, and educational level, among others. It is also crucial for a better design to take into account other more general but still relevant collectively shared characteristics. Such is the case of gender-based brain activity differences, which can help for a better understanding of gender-related risk factors inherent to brain disorders such as AD. Significant quantifiable differences between women’s and men’s brain activity in large healthy and clinical populations have been recently observed at 128 regions of the brain using functional SPECT (Single Photon Emission Computed Tomography) neuroimaging scans, in the largest functional brain imaging study conducted to date [Amen 2017]. Knowledge of specific brain activity

differences between women and men represents a crucial element for properly designing cognitive intervention protocols as well as for evaluating their ensuing results (Amen et al., 2017).

7.1.5. Accessibility Guidelines

A convenient way to address accessibility issues during computerized cognitive intervention design is to generally follow guidelines similar to the already proven W3C's World Wide Web Consortium (W3C) guidelines concerning Web accessibility of people with disabilities. Specifically interesting are strategies that address cognitive accessibility proposed in the Cognitive and Learning Disabilities Accessibility (COGA) guidelines, as well as physical and user interface accessibility proposed in the Web Content Accessibility Guidelines (WCAG 2.0). This section summarises the accessibility guidelines that we have formulated by adapting those recommended by the W3C that are relevant for our purposes.

7.1.5.1. Cognitive Accessibility

We recommend addressing cognitive disability-related accessibility issues during the design process of VR cognitive interventions following criteria similar to those defined in the “Techniques for The Cognitive and Learning Disabilities Accessibility Task Force (COGA)” (W3C, 2016).

Strategies to address users needs' are based on gap analyses (W3C, 2017b), of the type specified by industry and university experts within COGA. The process to identify and analyse such gaps should contain the following aspects:

- A background study, including an extensive review of research about users' specific cognitive disabilities, including challenges faced due to their impaired cognitive functions (W3C, 2015);

- Topics of logging in, security and safety, and how these issues could be affected by the cognitive disabilities (W3C, 2017a); and
- Authoring techniques (W3C, 2016).

We have formulated guidelines to be used to address cognitive disability-related accessibility issues by adapting the standard COGA guidelines to the design process of VR-based cognitive interventions. Table 7.1 summarizes some of these useful guidelines for several identifiable user's needs, indicating the corresponding usability strategies.

Technique	Usability strategy
Clear structure	<ul style="list-style-type: none"> ✓ Identify a few main tasks; ✓ Use single topic, idea, or short sentence: Time the event carefully; ✓ Allow for personalization: content should be user dependent; ✓ Provide easy to understand information; ✓ Distinctly portray clear and easy to understand graphic environment;
Style	<ul style="list-style-type: none"> ✓ Provide short and clear indications; ✓ Explain what outcomes to expect; ✓ Avoid visual metaphors; ✓ Use well known graphic symbols; ✓ Use simple movement;
Feedback	<ul style="list-style-type: none"> ✓ Provide rapid and direct sensory feedback;
Help meaning	<ul style="list-style-type: none"> ✓ Provide short info graphic tips; ✓ Use graphics to reinforce important issues; ✓ Use default formats (e.g. temperature, time, currency; etc.); ✓ Reinforce with graphics or symbols; ✓ If possible, provide speech support;
Clear design	<ul style="list-style-type: none"> ✓ Use clearly identifiable visual style for actionable items; ✓ Avoid difficult to see details; ✓ Highlight key issues: Place important features up front;
Complete and check	<ul style="list-style-type: none"> ✓ Prevent errors: Error correction should be transparent to user; ✓ Promote attention and focus: avoid distractions and interruptions; ✓ Allow for iterative design refinement

Table 7.1 – Some useful design guidelines to address cognitive disability-related accessibility issues.

7.1.5.2. *Physical Accessibility*

We recommend addressing physical accessibility issues during the design process of VR-based cognitive interventions following guidelines similar to those provided in WCAG 2.0 conformance levels (W3C, 2008) for Web accessibility. The conformance levels are determined according to the W3C by the increasing severity

of the criteria that must be satisfied: *Level A*, *Level AA*, and *Level AAA*. In general, each level satisfies the previous and its own requirements.

These conformance levels define four principles that constitute the basis of Web accessibility: *perceivable*, *operable*, *understandable*, and *robust*. These principles should be understood in the present case in reference to the possible physical disabilities resulting from the users' cognitive disabilities and other co-morbidities that might be present. Their meanings can be explained following the terms of the WCAG Principle of Accessibility guidelines (W3C, 2008), as follows:

- *Perceivable* - Information and user interface components must be presentable to users in ways they can perceive (they cannot be invisible to all of their senses)
- *Operable* - User interface components and navigation must be operable by users (the interface cannot require interaction that a user cannot perform).
- *Understandable* - Information and the operation of the user interface must be understandable (the content or operation cannot be beyond their understanding).
- *Robust* - Content must be robust enough that it can be interpreted reliably by a variety of user agents, including evolving assistive technologies (as technologies and user agents evolve, the content should remain accessible).

Table 7.2 summarizes some useful guidelines, indicating the corresponding purposes, to be used when addressing physical disability-related accessibility issues during VR-based cognitive intervention design. They are an adaptation of the standard WCAG guidelines.

Principles	Guideline	Purpose
Perceivable	G1.1 - Provide alternatives for content so that it can be changed into other forms according to user's needs.	Content that best circumvents user disability (e.g. enlarged scenario, louder sound, different sensory form).
	G1.2 - Provide alternatives for time-based media.	Access time-based and synchronized media. (e.g. audio, video, another sense, and combinations)
	G1.3 - Create content that can be presented in different ways without losing information or structure.	Ensure that all information is available in a form that can be perceived by all users.
	G1.4 - Make it easier for users to see and hear content including separating foreground from background.	Default presentation as easy to perceive as possible to people with disabilities.
Operable	G2.1 - Make all functionalities available regardless of physical disability	Interface through speech input, or any other kind of assistive technologies that can produce an output.
	G2.2 - Provide users enough time to find content.	Ensure completion of tasks at user's own pace.
	G2.3 - Do not include any content that is known to cause seizures.	Avoid the types of flash that are most likely to cause seizure when viewed even for a brief time.
	G2.4 - Provide ways to help users navigate, find content, and determine where they are.	Facilitate user's navigation and orientation and allow them to keep track of their location.
Understandable	G3.1 - Make graphics highly visible and understandable.	Allow graphic content to be seen with assistive technology.
	G3.2 - Make content appear and operate in predictable ways.	Presenting content in predictable order by making the behaviour of functional and interactive components predictable.
	G3.3 - Help users avoid and correct mistakes.	Reduce the number of errors that can be made, increase likelihood that errors will be noticed by users, and help them understand how to correct an error.
Robust	G4.1 - Maximize compatibility with current and future user agents, including assistive technologies.	Support compatibility with current and future user agents, especially assistive technologies.

Table 7.2 – Some useful design guidelines to address physical disability-related accessibility issues.

7.2.SWOT ANALYSIS

“Strengths–Weaknesses–Opportunities–Threats” (SWOT) analysis is a kind of assessment that can be used to help in identifying and defining key opportunities, weaknesses, challenges, and concerns that are relevant for understanding and assessing the applicability of VR-based solutions for cognitive disabilities care.

Such an SWOT analysis was conducted in the field of VR rehabilitation and therapy (Rizzo & Kim, 2005). Several capabilities of VR for rehabilitation and

therapy where identified in that study. Stimulus control and consistency, real-time feedback, safe testing, and motivation enhancement, are among those that were highlighted for their appealing potential. Also, some weaknesses and challenges associated to the characteristics of the specific rehabilitation and training target groups were identified in areas mainly related to the interface's design and the interaction methods, without seriously compromising the viability or the opportunities offered by VR technology in that field (Rizzo & Kim, 2005).

Following the concepts and strategies of a SWOT analysis, as previously described above and in Chapter 4, and considering the present state of affairs (described in Chapters 5 and 6), we have identified strengths, weaknesses, opportunities, and threats specifically related to the use of VR-based solutions for cognitive disability care. For the purpose of the present discussion, and as mentioned in Chapter 1, we understand that the expression “cognitive care” in general comprises actions involving diagnosis, prognosis, follow-up of cognitive impairment or decline; the mitigation of symptoms; the preservation, remediation or rehabilitation treatment, specially cognitive training; and including improvement of ADL performance to foster personal independence, active aging, QoC and QoL. Figure 7.3 shows the SWOT analysis matrix to be kept in mind while developing or designing VR cognitive interventions for MCI and ADRD.

STRENGTHS <ul style="list-style-type: none"> • Immersive and interactive; • Increased motivation and engagement; • Enhanced ecological validity; • Enhanced measurable effectiveness; • Real-time and long-lasting monitoring and feedback; • Online remote data access; • Enhanced data gathering options; • Reduced costs. 	WEAKNESSES <ul style="list-style-type: none"> • Technology resistance on the part of patients and caregivers; • Technological complexity; • Complicated multi-systemic interoperability; • Possible simulation sickness and other physiological effects;
OPPORTUNITIES <ul style="list-style-type: none"> • High potential of multisensorial emerging technology; • Personalization and self-adaptiveness; • Real-time data analysis and immediate feedback; • Improved testing and training; • Advanced cognitive disabilities care procedures. 	THREATS <ul style="list-style-type: none"> • Relative scientific weakness of existing evidence that could affect adoption; • Non-existing or conflicting healthcare regulations and policies; • Interfering commercial business interests;

Figure 7.3 – SWOT analysis matrix of VR-based cognitive interventions

The following sub-sections will describe the specific SO, WO, Threats analyses, indicating the potential key contributions of VR's internal strengths and external opportunities, and at the same time overcoming internal weaknesses and external threads, all intended to optimize the impact and applicability of VR-based solutions for cognitive disabilities care.

7.2.1. Strengths-Opportunities (SO) analysis

Using internal strengths can allow to take advantage of external opportunities. We have identified the following external opportunities to be considered during design to potentiate the internal strengths of the intervention:

1. *Emerging Technologies*: The rapid growth of emerging technologies, such as: information technology, nanotechnology, biotechnology, cognitive science, psychotechnology, robotics, and artificial intelligence, as well as the cost reduction of VR technologies, solidly support the development of advanced, accessible, usable, and affordable solutions in the field of VR-based neurocognitive training (Rizzo & Kim, 2005).
2. *Improved Treatments, procedures and testing environments*: The strengths of VR-based solutions for cognitive disabilities care can take advantage of developing external opportunities related to the improvement of treatments, medical procedures and/or testing environments. Today's odorant delivery systems for VR environments that are already commercially available from various sources²⁸, allow easy implementation of olfactory dysfunction testing (Lafaille-Magnan et al., 2017), which seems to be a particularly promising biomarker of preclinical MCI and AD that can be used for detection and diagnostic purposes, as already explained in Section 2.4.3.1. Another real opportunity of today's cognitive disabilities care is the possibility of improving existing care procedures, as was mentioned in Chapter 6, by combining CCT interventions with other medical procedures, such as Transcranial Magnetic Stimulations (tMS), modern brain imaging methods, as well as by possibly using tele-rehabilitation techniques (Nguyen et al., 2017). This type of combinations lead to a better understanding and follow-up of the disease and, at the end, helps increase the availability of better diagnosis and prognosis criteria.

²⁸ <http://www.olorama.com/en/virtual-and-augmented-reality-with-smells/>

3. Ecological validity: – “the degree to which results obtained in controlled experimental conditions are related to those obtained in naturalistic environments” (Tupper & Cicerone, 1990) – of current cognitive training methods can be significantly enhanced using VR platforms for creating highly realistic simulated environments. This feature, together with the capacity of VR to gather real-time data to better measure effectiveness, represent very important strengths that VR is able to contribute to the improvement of cognitive disabilities care procedures (e.g. cognitive training, follow-up, mitigation of symptoms, etc.).
4. Real-time and long-lasting monitoring and feedback: Another very significant strength of VR technology is its ability to create systematic human testing, training and treatment environments (Rizzo & Kim, 2005), that inherently provide real-time and long-lasting monitoring and feedback. This characteristic allows to implement behavioural and interaction tracking analysis within the solution in order to collect relevant data about user’s performance, monitor cognitive training evolution, adapt the system on the basis of user’s performance (e.g. changing the level of difficulty, unlocking new interventions, etc.), as well as to analyse long-lasting collected data in order to define new diagnosis and prognosis criteria and methods.
5. Personalization and self-adaptive systems: The availability of simplified personal ICT devices, the improvement of processing power and graphics, as well as the current trend of taking into account universal design principles²⁹ during design and development processes, has created a

²⁹ <http://universaldesign.ie/What-is-Universal-Design/The-7-Principles/>

propensity to develop accessible commercial software. Current trends of personalization and self-adaptive systems also point towards the design of VR-based cognitive training solutions that can meet the specific and changing requirements of ADRD patients and professional caregivers. By using the advantages of VR, personalized and adaptive scenarios can be created that are based on computational intelligence, real-time monitoring and data analysis, software flexibility, and the increasing development of innovative easy-to-use and user friendly devices (e.g. HMD, AR devices, Leap sensor, Kinect sensor, etc.) (Vaughan, Gabrys, & Dubey, 2016). This key characteristic of VR allows the follow-up of user's evolution and to progressively adapt the system to their specific care needs at every stage of the disease.

6. Motivation and engagement: the continuous and long-term use of any ICT solution is closely related to motivation and engagement. Treatment engagement in people with ADRD is crucial for the success of any cognitive training intervention. VR technology provides possibilities to enhance motivation and engagement, for example by using gamification techniques (e.g. rewards, levelling, challenges, timely assistance, etc.).
7. Reduced costs: VR capacity to reproduce and simulate different real-life environments represents an important factor in the reduction of costs related to therapy, rehabilitation or cognitive training programs, in which “natural / day-to-day” environments, conditions, and situations are key parts of the program. Virtual environments offer the possibility to: (a) be duplicated and distributed; (b) provide home-based care programs that could enhance user's participation in therapy/training programs; (c) improve the outcomes; (d) increase treatment adherence; and (e) reduce

costs related to the daily trip to specialized centres to comply with treatment or evaluate the evolution of the disease (Rizzo & Kim, 2005).

7.2.2. Weaknesses-Opportunities (WO) analysis

Using external opportunities can minimize the severity and alleviate the internal weaknesses of the design. Identified weaknesses of VR applicability in cognitive disabilities care are related to technological issues (e.g. complexity, graphics, type of interaction, interoperability, etc.) that represent a barrier for the adoption of VR-based solutions. The proliferation of innovative and advanced technologies could play an important role to reduce the impact of internal weaknesses. We have identified the following internal weaknesses to be considered and addressed during design through external opportunities:

1. Resistance to technology due the characteristics and needs of the specific target group, which combines age-related issues and ADRD symptoms.
2. Technology complexity that could impact on people's acceptance and disposition to use VR systems.
3. Simulation effects, such as cyber-sickness and other physiological effects. Some people might experience some kind of VR-related illness while using full-immersive VR-based solutions. Cyber-sickness or simulation sickness is known as "*a form of motion sickness with symptoms reported to include nausea, vomiting, eyestrain, disorientation, ataxia, and vertigo*" (Kennedy, Berbaum, & Drexler, 1994). The manifestation of such side-effects of this and other kinds depends on diverse factors such as: type of VE used, technical and graphic levels, exposure time, level of active interaction, presence of very rapidly changing visual images or effects, etc. More studies should be conducted in order to assess the occurrence of

side-effects to determine ways to avoid or minimize them (Rizzo, Schultheis, & Rothbaum, 2002).

4. Interoperability problems when trying to integrate different advanced devices and systems. For example, when easy-to-use interface devices need to be incorporated to address user's special needs or accessibility issues, or while having to integrate multisensory and multimodal experiences.

7.2.3. Threats analysis

Deficient scientific validation impacts adoption of VR-based solutions in cognitive disabilities care. Not having unified criteria during development and evaluation, as we discussed in Chapter 6, complicates validation. The weakness of some of the existing scientific evidence of training effectiveness, as well as the lack of enough proof of successful far transfer also affects development. Absence of common healthcare regulations and policies on the matter also affects the smooth progress of the developmental process. Commercial business interest in VR-solutions for cognitive disabilities care are also perturbing factors to take into consideration. These problems, originated mostly from methodological issues, should be addressed early by the development and design teams, to establish scientifically sound measures of objective evaluation, and by using standard design methodologies (Allaire et al., 2014; McCabe, Redick, & Engle, 2016; Simons et al., 2016). The following is a summary of suggestions and best practices to help overcome some of the presently worst scientific validation weakness of VR-based cognitive interventions:

- Objectively compare the relative merits of semi- and fully-immersive VR techniques, not only with respect to the resulting effectiveness, but also

regarding other factors such as ease of patient use, technical complexity, infrastructure needed, costs of installation and usage, etc.;

- Evaluate and objectively measure the capacity of outcomes’ “far transfer” to different scenarios;
- Follow-up and objectively measure the long-term endurance of VR-based CT outcomes;
- Carry out large size randomized controlled trials (RCTs) using scientifically rigorous and reliable safeguards (Button et al., 2013);
- Rule out or correct possible misleading placebo effects.

Internal strengths such as: (a) improvement of ecological validity through the use of VEs; (b) greater potential for data gathering, real-time monitoring and feedback collection; and (c) possibilities to conduct long-lasting monitoring of test results, together with the use of common definitions of best practices to conduct validation studies, will help to avoid or mitigate some of these external threats.

7.3.FRAMEWORK DEFINITION

As with any other high value-added product/service system, VR-based cognitive health intervention systems and applications pose very significant challenges in their design (Song & Sakao, 2017). The need to combine neurocognitive science and psychological practice with computational technology and digital graphic rendering methods, the potential conflicts between different technical specifications that generally show up in the early conceptual design phase, the emergence of hidden requirements or incompatibilities that come to light late or only during actual usage, the high level of design flexibility that is required, and the inherently high complexity of the emerging technologies involved, are the most relevant challenges of the

compendium of enormous difficulties faced when designing VR-based neurocognitive intervention applications.

With such difficulties in mind, and building upon the accumulated know-how derived from many previous works, we propose the use of a comprehensive methodological framework to steer the design of computerized cognitive interventions for cognitive disabilities care to be applied within VR-based environments. The proposed design frame of reference is intended to reduce possible design errors and deficiencies by systematically providing effective guidance to developers and designers. It supplies helpful methodological support based on standardized best practice guidelines. An accompanying roadmap directs design actions from the initial conceptual design phases of goal identification and requirement specification, to the final implementation phases of application configuration and performance testing, including the necessary provisions for data acquisition and analysis. The proposed framework remains flexible during the entire design process in order to adapt to user needs.

This proposed framework is not a fixed entity. Rather, it can be progressively refined and adapted by successive improvement through repeated optimization revisions. Such revisions will be based on routine feedback from designers, academic experts, and health care practitioners; but also will be triggered by the continuing emergence of more advanced and capable ICT tools and platforms, as well as by the substantial discoveries that are expected to occur within the neurocognitive sciences in the near future.

7.3.1. Framework Scope and Features

Based on the just discussed considerations and given the present state of affairs regarding the field of neurocognitive training interventions, we describe below

a methodological design framework to help the development and design of future VR-based solutions for cognitive disabilities care of people with ADRD. The proposed methodological framework applies to the design of VR-based cognitive interventions intended for any or all of the following uses:

- e. Reliably and objectively detecting and assessing cognitive impairment symptoms during the early MCI stages of AD, and subsequently monitoring the course of cognitive decline;
- f. Cognitive training of patients to mitigate the effects of ADRD symptoms on their Activities of Daily Living (ADL) and QoL;
- g. Researching and testing possible AD-associated indicators whose assessment could be implemented in novel VR-based diagnostic and prognostic instrumental procedures to detect and foresee the progression of early signs of AD; and
- h. Providing feedback from the VR-based cognitive intervention, which can be used to refine and improve its own operation and effectiveness through epistemic iteration, as well as to provide valuable information to extend the knowledge base that supports this multidisciplinary technology.

A design framework such as the one proposed here should have some general features necessary to help and enhance the development and design processes. Among these features the most significant are:

- 1. Provide a systematic frame of reference to assist in design conceptualization and definition of the intended goals and the required specifications;
- 2. Draw a clear roadmap to move through the different stages of the entire design process on the basis of standardized references;

3. Effectively coordinate and integrate the interaction between diverse requirements that belong to different knowledge domains (cognitive neuroscience, human health care, electronics engineering, computer technology, information systems, etc.)
4. Arrange for flexible customization of components to be able to adapt to different user needs;
5. Anticipate any potential initial conflicts between design specifications, and facilitate their early resolution;
6. Formulate specific measures and means for comprehensive and reliable assessment of the design;
7. Provide for iterative correction of deficiencies that may be uncovered at late stages, or during testing or even actual use;
8. Organize a process of design optimization through regular revision.

The proposed framework also is supposed to help in answering the following design expectations, concerns and considerations, divided here into five main categories: (1) expected benefits; (2) desired technical features; (3) main ethical challenges; (4) tasks needed for a better assessment and analysis; and (5) further research areas, which are summarised in Figure 7.4.

1. Expected Benefits	
<ul style="list-style-type: none"> • Improvement of patient experience (Higher sense of presence); • Increased patient motivational engagement; • Enhanced measurable effectiveness; • Better monitoring and feedback capabilities; 	<ul style="list-style-type: none"> • Greater information gathering; • Better transfer of training outcomes to other activities; • Longer lasting endurance of effects; • Better utilization of human and material resources; • Reduced costs.
2. Desired Technical Features	3. Main Technical Challenges
<ul style="list-style-type: none"> • Technological friendliness (ease of use); • Transparency of the technological platform; • Preservation of privacy; • Utilization with and without human supervision; • Capacity for remote delivery and monitoring (Telemedicine); • Ease and affordability of transfer from lab to clinical and home environments.; • Longer lasting training periods to enhance production of more evident effects. 	<ul style="list-style-type: none"> • Patient resistance to technology; • Far transfer and time endurance of outcomes; • Synergic design of multi-domain and multi-modality training exercises; • Technological complexity; • Security; • Multisystem interoperability; • Cross-professional collaboration on development and evaluation.
4. Tasks needed for a better assessment and analysis	
<ul style="list-style-type: none"> • Objectively compare the relative merits of semi- and fully-immersive VR techniques, not only with respect to the resulting effectiveness, but also regarding other factors such as ease of patient use, technical complexity, infrastructure needed, costs of installation and usage, etc.; • Evaluate and objectively measure the capacity of outcomes' "far transfer" to different scenarios; • Follow-up and objectively measure the long-term endurance of CT outcomes; • Carry out more and larger size randomized controlled trials (RCTs) using scientifically rigorous reliable safeguards; • Rule out or correct possible misleading placebo effects. 	
5. Further Research Areas	
Study multimodal interventions and other excitatory-type neurotechnological minimally-invasive interventions, such as transcranial electric or magnetic stimulation.	

Figure 7.4 –Expectations, concerns and considerations of the VR cognitive intervention design.

7.3.2. Framework phases

We have defined a methodological design framework composed of three main design phases: (1) conceptualization phase; (2) resources and system implementation; and (3) evaluation phase, as shown in Figure 7.5. The components related to each one of the framework phases are identified as basic components (green boxes), which comprise: the target group, purpose, research questions/variables, and context factors; and the evaluation components (blue boxes) such as: the previous knowledge and the data collection and evaluation approaches.

Figure 7.5 – Methodological Design Framework components.

7.3.2.1. *Conceptualization phase*

This first phase comprises the components related to the specific problem to be addressed, such as: barriers, goals, user needs and characteristics that will help in the definition of the user profile and the usage cases. This phase also comprises the analysis of previous specific knowledge, general know-how, and the most common existing guidelines in order to ensure that the designs, developments and evaluations are made by following an evidence-based approach.

One very important aspect to bear in mind when designing VR-based solutions for older people with ADRD, is the presence of comorbidities: physiological processes related to aging (e.g. presbyopia, osteoarthritic, decreased agility and responsiveness reflex, etc.) as well as, more specifically, those that arise as a result of the neurodegenerative disease itself (Monteagudo Peña, 2012). These issues interfere in the acceptance of the solution of the technology, as well as in the user's interaction. In those cases, the usability and accessibility and criteria already discussed should be included during the design and development process, in order to produce friendly, easy-to-use, safe and intuitive ICT solutions.

During the early stages of AD cognitive and functional deficits might be still not well manifested. However, the possibility of some functional impairments must be considered, such as: memory changes, difficulties in planning or solving problems, disorientation, difficulties understanding visual images and spatial relationships, problems with writing and speaking, misplacing things, poor judgement, changes in mood and personality, etc. (Alzheimer’s Association, 2017).

Unfortunately the deficits in memory and communication skills, produced by the cognitive degeneration, will make the use of VR-based platforms more difficult. For example, alteration of episodic memory affects the verbal and visual capacity of people with ADRD. However, other memory types such as semantic and procedural memory, seem to be preserved in the initial phases of AD (National Institute of Health, 2016).

Regarding technological acceptance, most older people, even if healthy, will experience difficulties using ICTs in general (Ma, Chen, Chan, & Teh, 2015), and VR technology in particular. Although there are not too many studies that focus on technological acceptance by people with ADRD, there have been some studies on the topic. They reported that, contrary to commonly held views, older people in general have positive opinions about new technologies (Chen & Chan, 2011), whenever the technology addresses their needs and is perceived as being easy to use.

7.3.2.2. *Resources and System Implementation phase*

This second phase pertains to the resources and system implementation of the VR-based cognitive intervention solution, as related to the actual components that define the following intervention’s aspects:

- concepts: user profiles, use cases, and variables;

- application category: cognitive diagnosis and impairment assessment; cognitive training for possible cognitive function improvement; and symptom mitigation, and behavioural remediation;
- type of sensory content (e.g. visual, audio, kinetic, etc.);
- technological aspects: technologies used, data collection methods, security, interaction mechanisms, safety;
- and ethics and legal aspects that might be involved.

Researchers and developers nowadays are incorporating new paradigms into their repertoire of service personalization tools, in addition to users' self-customization. These new paradigms gravitate around the perspective of an inclusive and universal design concept to satisfy the needs and requirements of particular groups of users, such as the elderly and people with disabilities, which is precisely the nature of the group we are particularly interested in. The use of inclusive and universal design techniques and tools in an adequate manner will help to provide solutions adequate to the particular problems that these users have to confront when using today's ICT systems and applications (United Nations, 2006; Wagner, Hassanein, & Head, 2010b).

As we already mentioned, some of these problems are related to usability issues, such as: functional limitations, behavioural and cognitive limitations, reduced capabilities, etc., which could strongly influence user acceptance (Eberle et al., 2011; LeRouge et al., 2013b). Both the elderly and cognitively impaired people have needs and concerns different from those of general users, on account of their cognitive and physical impairments, stemming from aging or from an existing disability. Unfortunately, such special needs and concerns are easy to be ignored at times during development and design processes (LeRouge et al., 2013b). It is therefore imperative to keep in mind at all times that the capabilities and conditions of these group of users

differ from those of other users, that the usability problems derived from those differences must be addressed, that these users react differently towards technology, and consequently that the interventions must be designed to be made more usable for them (Wagner et al., 2010b).

Various studies have been carried out and developments made to overcome several of the technological barriers faced by users affected by specific impairments or limitations, taking into account their particular characteristics and needs (Alm & Nakamura, 2001; Gregor et al., 2002; LeRouge et al., 2013b; Newell & Gregor, 1997b). In 2001 Fischer (Fischer, 2001) proposed to specifically classify users into different kinds, with respect to particular needs and characteristics, and within various environments. But a classification of users merely according to their expertise and knowledge (e.g., novel, intermediate, and expert) is not enough. In 2002 Gregor et al. (Gregor et al., 2002) presented a discussion about the particular issues involved in the design process of ICT solutions specifically geared to elderly users. They identified some relevant abilities that must be considered during the design process, such as: physical, sensory, and cognitive abilities; learning capacity; memory problems; environmental factors; and accumulated experience (Gregor et al., 2002).

When designing cognitive training interventions, motivational deficits that are present in many patients with MCI must be taken seriously into consideration from the start, because maintaining high levels of motivation and engagement are essential conditions for the success of the intervention. In addition of the enhanced engagement that results from the use of immersive VR, gamification of the training exercise itself can be very useful. Gamification means to design the training exercise as an attractive game to help minimize or disguise boring activities and to bring high levels of enjoyment into the exercise. This in turn promotes patient motivation and translates into significant improvement of training engagement in patients with MCI.

Gamification of cognitive training has been used for some time in many of the commercially available brain training products, and it continues to be used in interventions developed for all kinds of platforms. A recent example of gamification is a novel memory training game based on the iPad platform that produced improvements in the episodic memory of patients with aMCI (Savulich et al., 2017).

Ethical and legal aspects should be taken into account when designing, implementing and assessing ICT solutions. The main ethical issues in ICT that should be addressed are: (1) data protection and security; (2) data confidentiality; (3) information property; (4) authenticity, accuracy and fidelity of information; (5), informed consent of participants (for the evaluation phase). The EU commission has prepared a set of guidelines that includes questions to address identification issues, directions and major concepts of data protection and privacy, and provides a general overview of the main parameters and action suggestions (Charitidis et al., 2009). Similarly, the American Psychological Association (APA) recently published a set of guidelines for the evaluation of dementia and age-related cognitive change. This guide is a useful instrument when designing ICT-based solutions for the follow-up of the ADRD evolution (APA, 2012).

The use of VR-based solutions also adds more ethical considerations when involving some population groups (Mourant & Kennedy, 1998). For example, the already mentioned particular threats of VR exposure, such as cyber-sickness, should be given special consideration, although in some cases threats may not be an issue (Rizzo et al., 2002). In a recent study about ethical considerations for the use of VR in psychological sciences, Rizzo et al. proposed that screening procedures to identify possible side effects of VR, such as the Simulator Sickness Questionnaire (Kennedy et al., 1994; Kennedy, Lane, Berbaum, & Lilienthal, 1993), should be included in all VR protocols. Most vulnerable groups (e.g. impaired awareness, psychiatric patients,

etc.) should be identified in order to be aware of possible design additions to minimize risks.

7.3.2.3. *Evaluation phase*

The final phase involves specifying the evaluation approach, which includes the definition of the test environment, the data analysis methodology, and the identification of the limitations of the study that yield new challenges and new problem statements.

Handling the assessment of VR-based cognitive intervention designs as a mere technical task is inadvisable. Even if the results of such narrow-view evaluation were sound, they could turn out to be mostly irrelevant if the evaluation ignores the central issue, which is the intended human health benefit inherent to the intervention. No statistical analysis of results can be better than the design of the study that generated the results data. Likewise, no research design can be better than the foundation of the underlying theory or phenomenon (Fiedler, 2017).

A more meaningful evaluation strategy is to embrace a holistic view of the type that has been proposed for health information systems (HIS) design evaluation (Andargoli, Scheepers, Rajendran, & Sohal, 2017). Accordingly, we suggest that the integral evaluation of the VR-based cognitive intervention design should be conducted in an interpretive manner, guided by the following fundamental questions: Who does the evaluation? Why is it being done? How is it carried out? When should it take place? And finally, what is being evaluated? These basic questions conform the three fundamental interpretive premises, known as CCP, upon which the integral evaluation should be grounded: (1) Context ('who' and 'why'); (2) Process ('how' and 'when'); and (3) Content ('what') (Stockdale & Standing, 2006). The effectiveness and performance evaluation of a design framework such as this should

be carried out also using semi-structured interviews of designers, including their formal evaluation, adhering to appropriate comparison criteria (Song & Sakao, 2017).

If any test is to be conducted for design evaluation purposes using real users, it is important to clearly define the test approach to be followed, including, for example: sample size, exclusion/inclusion criteria, test groups, test environments, etc. A randomized controlled trial (RCT) (Button et al., 2013) is one of the most used standards for the evaluation of healthcare interventions. Nevertheless, it should be well designed, conducted, and reported to avoid biased outcomes by appropriately and rigorously follow a methodological approach. Also reporting the procedures and outcomes of an RCT should be done in an adequate and easy-to-follow way in order to give the appropriate information to be able to replicate the study and, in that way, enhance the possibilities of improve the scientific validity of the study. This important concern regarding the design, methodology and reporting of RCTs has been addressed by the Consolidated Standards of Reporting Trials (CONSORT) group in their statement for improve the reporting quality of RCT, updated in 2010 (Schulz, Altman, Moher, & CONSORT group, 2010). The CONSORT evidence-based minimum set of recommendations document contains guidance for design, conduction and reporting of certain types of RCTs, as well as for other trial designs (e.g. cluster randomised trials) that can be found in CONSORT extensions³⁰.

The following are recommendations from CONSORT group regarding the definition of the evaluation protocol that are most relevant for VR-based cognitive intervention design evaluation purposes:

- Allocate both active (fake training) and passive (no training) control groups to be able to accurately analyse resulting evidence.

³⁰ <http://www.consort-statement.org/extensions>

- An eligibility criteria for participants should be defined by (1) identifying the nature and stage of the disease being studied; (2) exclusion of persons thought to be particularly vulnerable to harm from the intervention; and (3) following the pertinent legal normative and accepted ethical principles. Obtaining informed consent of participants.
- Identify and describe the settings and locations where the data will be collected such as: where participants will be recruited, social, economic, and cultural environment, etc.
- Establish the method for sample size calculation.
- Assign participants to each comparison group using an unpredictable random process. Such method has been successfully used in trials for more than half a century (Forbes & Holt, 1948).

A full list of recommendations for design, conduction and reporting of RCT can be found at the CONSORT group Web page³¹, as well as in their publications (Moher et al., 2012; Schulz et al., 2010). Figure 7.6 shows a flow diagram template as proposed in the CONSORT statement for reporting the progress of all participants through the trial.

³¹ <http://www.consort-statement.org/checklists>

Figure 7.6 – CONSORT flow diagram template

There remains a need particularly driven by the still ongoing debate about the utility of commercial brain training products (discussed in Chapter 6), to fully demonstrate and validate beyond any reasonable doubt whether there is actual skill transference from cognitive training to real-life tasks, and, if any, the persistence in time of such transference. In this regard, there was a report of Committee on the Public Health Dimension of Cognitive Aging of the US Academy of Medicine (formerly called Institute of Medicine of the US Academies) that recommended specific criteria useful to evaluate the effectiveness of cognitive training programs (Blazer et al., 2015). These criteria can be translated into some practical guidelines to assess the far transfer issue in VR-based cognitive interventions. In the first place, one should ascertain how long trained skills are retained. Then, look into whether any transfer of training to other tasks that measure the same cognitive construct as the trained task, or to tasks relevant to the real world, have been reliably demonstrated. As just explained above, the evaluation of performance must use an active control

group whose members have the same expectations of cognitive benefits as the members of the experimental group. Finally, one must inquire whether the alleged benefits of the training product have been replicated by other research groups or by controlled clinical trials.

7.3.3. Schematic Functional Framework and Roadmap

As we have just described, the proposed methodological design framework is composed of three main phases: (1) conceptualization; (2) resources & system implementation; and (3) evaluation. These phases are explicitly reflected in the ensuing procedural roadmap which we have formulated on the basis of Latham's concepts and approach (Latham, 2014). They are complemented by other very important component aspects that intervene and significantly influence the development, design and testing processes of VR-based solutions for people with ADRD. As already mentioned in Chapter 4, these components are closely related to: 1) Personal user needs in terms of comprehensibility, accessibility, usability, safety, etc. 2) The type of technology used. 3) The interaction techniques involved. 4) Privacy and data security concerns. 5) Ethical and legal aspects.

Figure 7.7 shows an overall schematic view of the proposed functional methodological design framework. We have adapted some components originally proposed by Latham in order to include aspects related to our design process.

Figure 7.7 – Overall schematic view of the functional Framework

Specifically we have adapted the “Overall Approach” component of Latham and revised its name to “Design and Implementation.” The “Data Analysis” component, has been replaced by the evaluation phase, renamed here as “Assessment.” The interrelations between each of the modules and components of the framework, shown as arrows, guide the design process from problem conception to the final desired outcome. The modules in green forming a “T” represent the conceptualization phase, while the ones in blue forming a “U” are part of the two remaining phases: the resources and system implementation phase, and the evaluation phase. All components are connected within the “conceptual framework” in order to

allow progressive refinement and adaptation based on outcome evaluation and user's feedback.

The proposed methodological design framework is finally depicted in the form of a roadmap in

Figure 7.8. This roadmap contains the three defined main phases (conceptualization, resources & system implementation, and evaluation) as well as the relationships between their components. The red dashed square encloses the components related to the conceptualisation and implementation phases. After the system is implemented, the evaluation phase starts by defining the evaluation approach on the basis of the goals, objectives and predefined requirements, followed by data acquisition and analysis. Thereafter comes the performance testing and the

holistic evaluation. Once the outcomes have been analysed and the evaluation has been completed, a methodological feedback route is provided to perform optimization and refinement of the intervention, whenever necessary. Both system conceptualization and/or its implementation phases may be refined to optimise the design.

Figure 7.8 – Framework Roadmap

We have defined a methodological design framework for VR-based neurocognitive interventions based on the analysis of the current state of the art, the scientific validity, and the clinical relevance of such VR-based interventions. The proposed framework is a useful contribution to guide and assist multidisciplinary

research, development and design aimed to address the care of ADRD patients, fostering the improvement of their QoC and QoL through the use of modern VR technologies. The framework includes relevant methodology, design best practices and guidelines, as well as a matching functional roadmap. The proposed methodological design framework is rooted in and informed by our knowledge, understanding, and thorough analysis of the soundest evidence available on the subject. Meticulous explanations of the motivations appropriately complement the ensuing suggestions, recommendations, and guidelines.

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CHAPTER 8

FINAL DISCUSSION AND CONCLUSIONS

The WHO Global Action Plan on the Public Health Response to Dementia (2017–2025), endorsed at the 2017 World Health Assembly on 03 April 2017, calls on governments of member states to promote action plans for dementia, drawing on the latest evidence to tackle the impending dementia crisis. Among the proposed actions for member states regarding the promotion of research activities are:

“Develop, implement and monitor the realization of a national research agenda on prevention, diagnosis, treatment and care of people with dementia in collaboration with academic and research institutions,” “Increase investment in dementia research and innovative health technologies...”

“...allocate budgets to promote projects that: support collaborative national and international research; promote sharing of and open access to research data; generate knowledge on how to translate what is already known about dementia into action; and support the retention of the research workforce...” and

“Foster the development of technological innovations that, in terms of design and evaluation, respond to the physical, psychological and social needs of people with dementia, their carers or people at risk of developing dementia; these innovations include but are not limited to diagnosis, disease monitoring and assessment, assistive technologies” (WHO, 2017).

The pressing demand for improving the quality and efficacy of health care and social support services for the world’s growing elderly population, is becoming critical in the case of those affected by ADRD. While age-related progressive neurodegenerative cognitive disorders continue to place an ever growing human and economic burden on the global society, ICT-based applications have the potential to

make an enormous positive impact to revert this trend through the widespread use of computerized diagnostic and therapeutic interventions. Such applications may be readily modified, scaled, and adapted to address the diverse conditions, peculiarities and needs of mental health preservation all over the world. ICT-based tools will undoubtedly play a vital role in an increasingly digital mental health-care future. But that game-changing effect can happen only if engineers and mental health professionals join forces to face the challenge together (Torous, 2017). It is clear that the road to achieve that goal will be made significantly easier by the deployment of innovative, computer-based ICT applications capable of addressing the specific needs of cognitive impairment diagnosis, monitoring, mitigation and rehabilitation.

Research, design, development, and implementation of VR-based neurocognitive interventions particularly aimed at the care of people affected by age-related cognitive impairments, directly addresses also several important elements of the European Parliament resolution of the European initiative on AD and other dementias³². Specifically, the use of VR-based CT systems will:

- provide effective support to patients with ADRD and their caregivers to enhance the QoL of these patients in their familiar environment;
- place a particular focus on appropriate therapeutic interventions for the pre-dementia phase of AD to slow down its progression;
- provide effective training interventions to mitigate the symptoms of patients with MCI and early-stage AD; and

³² European Parliament. European initiative on Alzheimer's disease and other dementias. 2010. Available in: <http://www.europarl.europa.eu/sides/getDoc.do?type%4REPORT&reference%4A7-2010-0366&format%4XML&language%4EN>. Accessed February 08, 2014.

- introduce novel multidisciplinary approaches to foster the cross-feeding enrichment of knowledge for ADRD prevention, diagnosis, treatment, and care.

Within such general context, in this thesis we have attempted to provide a clear perspective viewpoint about the use of VR tools for cognitive disabilities care, meant to assist medical personnel, health care workers, and other caregivers in improving the QoC and QoL of people living with ADRD. We also discussed effective design criteria and developmental strategies and suggested some possibly useful protocols and procedures. The particular innovative supportive advantages offered by the immersive interactive characteristics inherent to VR technology were also analysed and discussed.

A brief appraisal of recent and current VR technology use in ADRD applications was offered in Chapter 5, categorizing them according to their intended purpose, focus feature, methodology employed, immersion level, and passive or active interaction. Our critical assessment exposed and highlighted the fact that to date most VR-based cognitive interventions still do not yet make use or take full advantage of advanced VEs with a high level of immersion and interaction. We emphasised that most, if not all, of these applications rely on conventional or antiquated interface and display technology, concluding that substantial improvements are needed if VR is to become a useful platform for better and more versatile assessment and computerised training tools for ADRD. Use of the latest display technologies available, such as advanced emerging head-mounted displays and 3D smart TV technologies, together with realistic multi-sensorial interaction devices, such as haptic and olfactory capacities, as well as concurrent neuro-physiological feedback capacity, are some of the most beneficial improvements we suggest. Additionally, we consider that it is important that future VR applications for

ADRD, if they are ever to make a meaningful social and human impact, must be designed to be easily and affordably transferable to in-home and nursing home environments.

During the course of this work, we consistently noticed that the overall efficacy of existing VR-based interventions for CT is frequently difficult to establish on the basis of results gathered from assessments and clinical trials. It became evident to us after exhaustive examination of numerous individual studies and relevant systematic reviews and meta-analyses that this uncertainty derives mostly from: the lack of consistent methodologies across trials and VR systems, absence of generalizable results, and the existence of many uncoordinated efforts of individual heterogeneous studies. Therefore, we join others in suggesting the development of methodological and technical common procedures for VR cognitive interventions (Ortiz-Catalan et al., 2015).

As with other technologically-based solutions for health care, a particular feature of developing VR-based cognitive interventions for ADRD is the reliance on intense multidisciplinary collaboration. A combined effort on the part of ICT engineers and neurocognitive specialists is indispensable during the conceptual and system design phases. Involvement of physicians, technical specialists, caregivers, and patients at other stages is also necessary. A more comprehensive and far-reaching aspect of developmental VR-based technology solutions for neurocognitive intervention, which we have called attention to, is that they should serve also as experimental platforms to deliver timely information and useful feedback to clinicians and researchers.

We have also presented in Chapter 6, as an analytic narrative, a complete picture of the state of the art, challenges and perspectives of the field of ICT-based neurocognitive interventions for older adults. Our contribution is the particular focus

placed on applications aimed at MCI and ADRD cognitive deficits. We analysed computerised cognitive training in the context of the so called ‘brain training controversy,’ and provided clarifying explanations about the true nature and extent of this debate, which negatively affects the support given to R&D+i initiatives related to VR-based neurocognitive interventions. We proposed that, because of the still preliminary nature of most of the data currently available in this field, further research initiatives must be pursued in the quest for better verification of effectiveness. Our conclusions suggest that advanced ICT-based tools, especially VR, and AR, technologies, today represent the most appropriate platforms for applying non-pharmacological computerized interventions for mitigating the effects of ADRD-associated cognitive impairment.

However, it seems as if the development of computerised cognitive training tools has fallen into the perpetual common dilemma of scientific and technological research. This dilemma supposedly means having to satisfy requirements of being surprising, original and innovative, and at the same time being theoretically and methodologically sound, i.e. predictable and replicable (Fiedler, 2017). Within a framework of such hard choices, the real intrinsic purpose of conducting biomedical engineering research in this attractive but controversial area of ICT-based cognitive impairment mitigation, which is no other than to reduce human suffering and improving wellbeing, has been frequently eclipsed by extrinsic factors. The main culprit is the controversy about the scientific soundness of certain commercial brain training products, which has focused almost exclusively on rigorous statistical aspects and strict rule adherence considerations.

This lingering controversy about the reproducibility of findings, questionable research procedures, and potential inadequacy of statistical analyses attributed to many trial studies in this area of computerised brain training, must be put to rest by

future research, which need to be more replicable, reflective of a true effect, and based on reliable statistical evaluations. Notwithstanding the desirability of the application of such undisputable criteria in future trial studies, it is no less true that future research activities in this area of VR-based cognitive interventions for ADRD need to embrace a wider vision of the practical importance of pluralistic science, within which **exploratory phenomenon-driven research can play as much a constructive role as formal theory-testing type of research**. In that respect, it is wise to realise that as Klaus Fiedler says: “(I)t is *neither unscientific nor useless ... to tackle risky research topics for which no strictly theory-driven account is available (yet)*” (Fiedler, 2017).

Given of the inexistence to date of effective pharmacological disease-modifying treatments for AD, health-care systems worldwide and society in general are in serious danger of being economically and humanely overwhelmed by the expected costs and social burdens that caring for people with dementia could bring in the future, unless something is done soon (Frankish & Horton, 2017). Even if an effective pharmacological, or otherwise, therapy for AD were never found, its manifestations may be managed through different types of interventions that will help alleviate its symptoms. The Lancet Commission on Dementia Prevention, Intervention, and Care has very recently indicated, based on analysis of collected evidence, that new advances in the use of technological innovations could facilitate that individuals affected by ADRD live in safer, more stimulating, and better functionally adapted surroundings, and could as well assist care-givers to improve QoC (Livingston et al., 2017). Therefore, it seems convenient to diligently undertake actions on improving affordable prevention, intervention, and care through advanced VR and associated technologies, as they can considerably enrich the living conditions

of dementia patients and their families, thereby contributing to a significantly brighter future for society in general.

As a final note about the future role of ICT in the neurosciences, we wish to cite a recent insightful reflexion by Prof. Sophia Vinogradov, Head of the Department of Psychiatry at the University of Minnesota's Medical School. In a recently published comment (Vinogradov, 2017), she heralded an imminent paradigm change to be centred on the intensive use ICT-based tools. This opinion is grounded on her confidence that computational neuroscience and neuroplasticity-based therapy together represent the future of psychiatry. We hope that the present work has somehow contributed to advancing towards such worthy goal.

8.1. ACHIEVED OBJECTIVES IN RESPONSE TO RESEARCH QUESTIONS

Based on the work reported in this doctoral thesis, we summarize below how the specific objectives were met to answer the proposed research questions, as described in the methodological approach presented in Figure 4.1 of Chapter 4.

RQ1: Are ICT-based cognitive interventions scientifically regarded as useful tools for evaluation or treatment of the effects of cognitive impairment disabilities in patients with Alzheimer's disease or related dementias (ADRD)?

RQ2: Can the data collected from this type of computerized tools be useful and clinically relevant?

RQ1 was answered by achieving O1, which established the scientific validity of ICT VR-based solutions as tools for the monitoring and mitigation of cognitive disabilities' effects in ADRD care. Likewise, RQ2 was answered by achieving O2, which investigated if the data collected from ICT VR-based solutions for monitoring

and mitigation of cognitive disabilities' effects in ADRD care is clinically relevant. Both of these two questions were addressed in Chapters 5 and 6.

Chapter 5 presents a detailed literature review and analysis of VR use for detection and mitigation of the effects of cognitive impairment in MCI and ADRD patients. The most important studies reported in the specialized literature were grouped and categorised. Careful analysis ascertained the potential usefulness and exceptional opportunities of VR technology as a valuable tool for cognitive evaluation, monitoring, symptom mitigation, and training of people with ADRD-associated cognitive impairments. This is a widely held view shared by most specialists today, in spite of the fact that existing scientifically robust evidence about its efficacy, although abundant, is considered still unsatisfactory by some specialists.

Chapter 6 went deeper into this analysis and discussed the impact of the ongoing debate about commercial brain training products on the development of the cognitive training paradigm in general. We explained the negative effect that this debate is having on R&D+i activities and initiatives aimed at developing innovative VR-based neurocognitive interventions for ADRD patients. We explained why many studies conducted on about this topic are not considered by some experts as having reported unmistakably positive results, because they have failed to provide sufficient scientific evidence of their effectiveness. However, we argued that the lack of sufficient scientific evidence in some studies does not demonstrate by itself that the diagnostic or training protocol used is ineffective. Moreover when there are other studies by respectable specialists that do report clear evidence of effectiveness. We also indicated, in agreement with most specialists' opinions, that the lack of scientifically satisfactory evidence in reporting trial results in this area of research is often a consequence of methodological shortcomings, such as deficient experimental design, ineffective evaluation, inadequate statistical procedures, etc., We contend that

most of the present uncertainty issues about the efficacy of VR-based cognitive interventions should be overcome using more rigorous scientific methodological practices.

Our analysis indicates that VR-based cognitive interventions still need broader and deeper research. It also suggests that emerging neurocognitive know-how and innovative technology must be incorporated into these interventions to make the most of their ability to supply assistive support to clinicians and caregivers. Only doing so can the effectiveness of VR-based cognitive interventions be maximised to help in providing significant enhancement to the QoC and QoL of people living with ADRD and their families. Addition of highly immersive VEs should turn out to be an excellent means to improve the effectiveness of the interventions. Implementation of advanced VR-based cognitive interventions will also provide a way of reliably gathering useful data to systematically build data-bases that are indispensable for advancing the knowledge needed for future R&D+I in this field.

The ability to transfer the potential effects to other not-trained activity domains (far transfer capacity) was presented as a crucial aspect of any VR-based cognitive training interventions. We thus recommended that long-term follow-ups are indispensable to appraise the retention potential of the intervention effects. Although not yet fully demonstrated, we expect, by extrapolating VR experiences from other domains, that the use of VR in CT will in fact increase the probability of far transfer to real daily life situations. We have also pointed at evidence of other potential contributions of VR-based interventions in the realms of sensory perceptual abilities and long-term visual perceptual learning. We indicated that VR as well could become an important factor for further understanding of neuroplasticity (when used together with neuroimaging techniques), and perhaps be of future assistance in the development of model-based neuroscience.

RQ3: Considering the ongoing brain training debate, should R&D efforts in computerized cognitive training (CCT) interventions for ADRD continue to be pursued? Or for that same reason, should such activities be encouraged, supported or funded?

RQ3 was answered in an affirmative sense, thus achieving O3. The strengths and weakness of VR-based cognitive interventions applicability in cognitive disabilities care of ADRD were identified and assessed on the basis of the existing references and the analysis and discussion presented in Chapters 5 and 6, considering the quick evolution of emerging VR technologies. We rejected the contentions that all CCT interventions are ineffective or that cognitive function in general cannot be trained. In Chapter 6 we substantiated our point of view, and offered arguments for continuing to pursue and support R&D+i activities to improve the effectiveness of CCT interventions in general, and especially those based on VR aimed at ADRD.

From our analysis we were able to identify key opportunities, weaknesses, challenges, and concerns. A SWOT analysis was proposed in Chapter 7 as a valuable tool for understanding the applicability issues of VR-based solutions in cognitive disabilities care, were presented. The SWOT analysis was used as the basis to define the proposed methodological design framework.

RQ4: Under what conditions can VR-based intervention tools produce significantly effective results for detection or evaluation and for treatment or mitigation purposes of cognitive disabilities in ADRD patients?

RQ4 was answered by achieving O4, which assessed and established throughout Chapters 5 the roles that VR can play in the evaluation, monitoring and mitigation of the effects of cognitive impairment in ADRD patients. Special

consideration was given to advanced VR-based neurocognitive training type interventions. By carefully examining the current state of the art, we identified the different conditions that should be taken into consideration to produce significantly effective results. Among them are: the incorporation of innovative VR and other ICTs and emergent neurocognitive know-how, supplying assistive support to clinician and caregivers, timely gathering and transmission of relevant information, combining performance data with psycho-physiological data, and real-time feedback.

We also described in Chapter 6 the required characteristics and conditions that advanced VR-based cognitive interventions, need to fulfil in order to be able to induce significant, transferable and lasting beneficial effects in people with ADRD. They refer mostly to methodologies for carrying out trial studies in a scientifically rigorous manner, and to the involvement of multi-domain and multi-modality ICTs.

RQ5: It is possible to develop a specific set of general methodological guidelines that can be useful for assisting multidisciplinary R&D teams in the task of designing VR-based cognitive evaluation and treatment interventions for ADRD patients, aimed at improving their quality of care (QoC) and quality of life (QoL)?

RQ5 was answered by achieving O5 and O6. O5 analysed and assessed current methodologies and guidelines, users' needs, and possible technological and acceptance barriers specifically related to the use of ICT-based and VR-based systems in ADRD care. To accomplish O6 we have proposed in Chapter 7 a methodological design framework for VR-based cognitive interventions to be used for the following extended set of possible applications: (a) Cognitive training of MCI and ADRD patients to delay the onset or slow the progression of cognitive impairment symptoms, or at least mitigate their effects on ADL and QoL. (b) Reliable and objective initial detection and later monitoring of symptoms' evolution. (c) Searching for and

eventually examining possible novel, or understudied, indicators, which may then be supported within innovative VR-based systems, for use in diagnostic and prognostic instrumental procedures capable of detecting early signs of AD, and perhaps foreseeing the development of its progression. And (d) providing performance feedback to improve the intervention performance through epistemic iteration, and also to easily gather data to extend the knowledge base for future research.

In Chapter 7 we have also analysed existing design and evaluation guidelines previously reported in the literature, covering general ICT design process, design components specifically for people with cognitive disabilities, as well as evaluation methodologies and good practices. We also defined and described the concepts, components, and structure of our proposed methodological design framework, on the basis of the present state of affairs, as described in Chapters 5 and 6. The components are closely related to the scope defined in O6. Three types of components are included in the proposed framework. They are related to the conceptualization, resources and system implementation, and final evaluation phases. We have also proposed in Chapter 7 a schematic functional roadmap intended to aid in following the steps of the proposed methodological design framework.

8.2. ORIGINAL CONTRIBUTIONS

The most outstanding original contributions of the research work reported in this doctoral thesis are:

1. **A distinctive categorization of VR systems specifically designed for ADDR** according to: a) the intended purpose (e.g., cognitive impairment assessment and early diagnosis, patient cognitive training or rehabilitation, caregivers' education, etc.); b) the domain focus (e.g., spatial impairment, memory deficit, etc.); c) the type of methodology used (e.g., tasks, games,

mazes, etc.); d) the immersion level; e) the sensorial modalities used (e.g., visual, auditory, kinaesthetic, etc.); and f) the type of interaction (passive or active). This contribution is described in Chapter 5 – Section 5.3.

2. **An informed analysis of the current ‘brain training controversy,’ and its impact on the cognitive training paradigm**, focusing on the possible influence of this debate on R&D+i activities that involve innovative VR-based neurocognitive training interventions for ADRD. A complete critical analysis and discussion is presented in Chapter 6.
3. **An up-to-date identification and discussion of the main technical and scientific challenges** faced to develop effective VR-based neurocognitive interventions for ADRD, based on the most recent findings and our own informed analysis, as presented in Chapters 5 and 6. These technical and scientific challenges translate into characteristics and conditions needed to improve the potential effectiveness of VR-based tools for cognitive impairment care. They in turn are the basis for the customised methodological design framework that is proposed in Chapter 7.
4. **A novel methodological design framework for developing VR platforms to be used in cognitive disabilities care**, specifically for people with MCI and early stage ADRD. The description and explanation of the proposed framework, as well as its functional roadmap, are presented in Chapter 7.

8.3. FUTURE WORK

The Committee on the Public Health Dimension of Cognitive Aging of the Institute of Medicine (IoM) of the US Academies of Sciences, Engineering, and Medicine, nowadays known as the US National Academy of Medicine (NAM),

produced a report (Blazer, Yaffe, & Liverman, 2015) that included criteria for the improvement of research, evaluation and assessment processes related to cognitive training programs. We have analysed the proposed criteria and have extracted and adapted the most relevant recommendations pertinent to VR-based cognitive interventions, which are summarized in Table 8.1.

<i>Recommendation 1: Increase Research</i>	
<i>Expand research on the trajectories of cognitive aging and improve the tools used to assess cognitive changes and their effects on daily function.</i>	<ul style="list-style-type: none"> – Studies to examine the mechanisms underlying VR interventions that affect the cognitive trajectory; – Studies to identify and validate novel VR tools and measures of function that capture the complexities of real-world tasks and are sensitive to early changes in cognition and function;
<i>Recommendation 2: Collect and Disseminate Data</i>	
<i>Strengthen efforts to collect and disseminate population-based data on cognitive aging.</i>	<ul style="list-style-type: none"> – Data collection efforts and further analyses involving geographically diverse and high-risk populations; – Longitudinal assessments of changes in cognitive performance and risk behaviours in diverse populations.
<i>Recommendation 4: Promote Cognitive Decline Prevention</i>	
<i>Expand research on risk and protective factors, as well as on interventions aimed at preventing or reducing cognitive decline and maintaining cognitive health.</i>	<ul style="list-style-type: none"> – Maximize the comparability of data about risk and protective factors of cognitive aging, by promoting collaboration between longitudinal studies across life span; – Examine risk factors and interventions in under-studied and vulnerable populations; – Conduct scientifically solid single- and multicomponent trials of promising VR interventions to promote cognitive health and prevent its decline, testing for both cognitive status and functional outcomes. – Explore older adults' views regarding preservation of cognitive health, as well as specific preferences of VR-based cognitive interventions and training modalities; – Identify effective VR approaches to promote healthy cognition across the life span.
<i>Recommendation 5: Ensure veracity of claims</i>	
<i>Enact appropriate regulatory policies and guidelines for review, and approval.</i>	<ul style="list-style-type: none"> – For commercial products that may assert dubious claims about cognitive enhancement or maintaining cognitive abilities.

Table 8.1 – Summary of some criteria for furthering research, evaluation and assessment of cognitive training interventions.

In addition to these basic suggestions, it is important when assessing cognitive decline to determine the relationship between cognitive aging and functioning in activities of daily life (ADL), since changes in cognitive abilities will make a notable

impact on older people's ability to perform everyday tasks. Today there is also a need to try to manage as much as possible the adaptation of the elderly to new technologies that are an unavoidable part of modern living. A comprehensive and methodical research effort to understand their relationship and how cognitive decline affects older people's adaptability to new technology is needed. Further research on these basic issues related to the relation ability-performance is desirable.

Three other final suggestions of possible lines of action that came up during the execution of the present work are:

- Development of a computerized design roadmap guidance protocol tool, in the form of a software package, to manage the practical application of the proposed methodological framework's roadmap.
- Exploration and appraisal of the usefulness and potential viability of using multi-domain and multi-modal VR-based interventions, in conjunction with other excitatory-type neuro-technological minimally-invasive interventions, such as transcranial electric or magnetic stimulation techniques, and to research their potential contribution for increasing the effectiveness of VR-based neurocognitive training type of interventions.
- Further study and appraisal of the possible use of various sensorial dysfunctions as novel testing tools (biomarkers) to detect, diagnose or evaluate ADRD-associated cognitive impairment. One outstanding example is VR-based olfactory testing of intensity acuity or odour discriminatory ability.

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APPENDIX A

SCIENTIFIC PUBLICATIONS

Related Scientific Publications Directly Related to this Thesis

This section presents and ranks the four articles dealing with ICT-based interventions for cognitive impairment that have been published by Rebeca I. García-Betances as the first author. Each article is followed by a corresponding list of references that have cited them until 31 August 2017.

1. **García-Betances, R. I.**, Jiménez-Mixco, V., Arredondo, M. T., & Cabrera-Umpiérrez, M. F. (2015). Using virtual reality for cognitive training of the elderly. *American Journal of Alzheimer's Disease & Other Dementias*, 30(1), 49-54. <https://doi.org/10.1177/1533317514545866>.

Impact Factor (2015): 1.614; Q3 in Geriatrics & Gerontology.

- 1.1. Foloppe, Déborah A., Paul Richard, Takehiko Yamaguchi, Frédérique Etcharry-Bouyx, and Philippe Allain. "The potential of virtual reality-based training to enhance the functional autonomy of Alzheimer's disease patients in cooking activities: A single case study." *Neuropsychological rehabilitation* (20 Oct 2015): 1-25. <https://doi.org/10.1080/09602011.2015.1094394>
- 1.2. Serino, Silvia, and Elisa Pedroli. "Technology and Cognitive Empowerment for Healthy Elderly: The Link between Cognitive Skills Acquisition and Well-Being." Chapter 8 of *Integrating Technology in Positive Psychology Practice*, pp. 193-213, A volume in the Advances in Psychiatry, Mental Health, and Behavioral Studies Book Series, IGI Global Pub., Feb 2016. ISBN9781466699861. <https://doi.org/10.4018/978-1-4666-9986-1.ch008>

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<http://dx.doi.org/10.15503/jecs20161.75.91>
- 1.5. García-Casal, J. Antonio, Andrea Loizeau, Emese Csipke, Manuel Franco-Martín, M. Victoria Perea-Bartolomé, and Martin Orrell. "Computer-based cognitive interventions for people living with dementia: a systematic literature review and meta-analysis." *Aging & mental health*, vol. 21, no. 5 (2017): 454-467. <http://dx.doi.org/10.1080/13607863.2015.1132677>
- 1.6. Plata-Bello, Julio. "The Study of Action Observation Therapy in Neurological Diseases: A Few Technical Considerations." Chapter 1 of *Neurological Physical Therapy*, edited by Toshiaki Suzuki, InTech Pub., May 10, 2017. ISBN 978-953-51-3114-4. <http://dx.doi.org/10.5772/67651>
- 1.7. Martínez, María del Carmen Rodríguez, Ortega Fernández, Emilio and Sánchez Vega, Elena. "Aplicación de nuevas tecnologías en personas mayores con trastorno cognitivo leve-moderado desde la Terapia Ocupacional." *Innoeduca. International Journal of Technology and Educational Innovation*, vol. 3, no. 1 (May 2017): 75-84.
<http://dx.doi.org/10.24310/innoeduca.2017.v3i1.2037>
- 1.8. Arlati, Sara, Andrea Zangiacomi, Luca Greci, Simona Gabriella di Santo, Flaminia Franchini, and Marco Sacco. "Virtual Environments for Cognitive

and Physical Training in Elderly with Mild Cognitive Impairment: A Pilot Study." *In Augmented Reality, Virtual Reality, and Computer Graphics, Proceedings of the 4th International AVR Conference, Ugento, Italy, June 12–15, 2017, Part II*, pp. 86-106. A volume in the Lecture Notes in Computer Science Book Series, Springer, Cham, 2017. http://dx.doi.org/10.1007/978-3-319-60928-7_8

1.9. Caffò, Alessandro O., Lopez, Antonella, Spano, Giuseppina, Serino, Silvia, Cipresso, Pietro, and Stasolla, Pablo. "Spatial reorientation decline in aging: the combination of geometry and landmarks." *Journal of Aging & Mental Health*, pp. 1-12, Published online: 20 Jul 2017.

<http://dx.doi.org/10.1080/13607863.2017.1354973>

2. **García-Betances, R. I.**, Waldmeyer, M. T. A., Fico, G., & Cabrera-Umpiérrez, M. F. (2015). A succinct overview of virtual reality technology use in Alzheimer's disease. *Frontiers in aging neuroscience*, 7.

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Impact Factor (2015): 4.348; Q1 in Geriatrics & Gerontology, Q1 in Neurosciences.

- 2.1. Serino, Silvia, and Elisa Pedroli. "Technology and Cognitive Empowerment for Healthy Elderly: The Link between Cognitive Skills Acquisition and Well-Being." Chapter 8 of *Integrating Technology in Positive Psychology Practice*, pp. 193-213, A volume in the Advances in Psychiatry, Mental Health, and Behavioral Studies Book Series, IGI Global Pub., Feb 2016. ISBN9781466699861. <https://doi.org/10.4018/978-1-4666-9986-1.ch008>

- 2.2. Manera, Valeria, Emmanuelle Chapoulie, Jérémy Bourgeois, Rachid Guerchouche, Renaud David, Jan Ondrej, George Drettakis, and Philippe Robert. “A feasibility study with image-based rendered virtual reality in patients with mild cognitive impairment and dementia.” *PloS one*, vol. 11, no. 3 (18 Mar 2016): e0151487. <https://doi.org/10.1371/journal.pone.0151487>
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- 2.6. Lledó, Luis D., Jorge A. Díez, Arturo Bertomeu-Motos, Santiago Ezquerro, Francisco J. Badesa, José M. Sabater-Navarro, and Nicolás García-Aracil. “A comparative analysis of 2D and 3D tasks for virtual reality therapies based on robotic-assisted neurorehabilitation for post-stroke patients.” *Frontiers in aging neuroscience*, vol. 8 (26 Aug 2016): 205. <https://doi.org/10.3389/fnagi.2016.00205>

- 2.7. de la Torre-Luque, Alejandro, Luis Valero-Aguayo, and Ernesto J. de la Rubia-Cuestas. “Visuospatial Orientation Learning through Virtual Reality for People with Severe Disability.” *International Journal of Disability, Development and Education*, vol. 64, no. 4 (24 Jan 2017): 420-435.
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- 2.8. Lecouvey, Grégory, Julie Gonneaud, Pascale Piolino, Sophie Madeleine, Eric Orriols, Philippe Fleury, Francis Eustache, and Béatrice Desgranges. “Is binding decline the main source of the ageing effect on prospective memory? A ride in a virtual town.” *Socioaffective neuroscience & psychology*, vol 7, no. 1 (10 Apr 2017): 1304610.
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- 2.11. Del Felice, Alessandra, Marzia Alderighi, Matteo Martinato, Davide Grisafi, Anna Bosco, Pamela J. Thompson, Josemir W. Sander, and Stefano Masiero. “Memory Rehabilitation Strategies in Nonsurgical Temporal Lobe Epilepsy: A Review.” *American journal of physical medicine & rehabilitation*, vol. 96, no. 7 (Jul 2017): 506-514.
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- 2.12. Serino, Silvia, Elisa Pedroli, Cosimo Tuena, Gianluca De Leo, Marco Stramba-Badiale, Karine Goulene, Noemi G. Mariotti, and Giuseppe Riva.

“A Novel Virtual Reality-Based Training Protocol for the Enhancement of the ‘Mental Frame Syncing’ in Individuals with Alzheimer's Disease: A Development-of-Concept Trial.” *Frontiers in Aging Neuroscience*, vol. 9, p. 240, 27 July 2017. <http://dx.doi.org/10.3389/fnagi.2017.00240>

3. **García-Betances, R. I.**, Cabrera-Umpiérrez, M. F., Ottaviano, M., Pastorino, M., & Arredondo, M. T. (2016). Parametric cognitive modeling of information and computer technology usage by people with aging-and disability-derived functional impairments. *Sensors*, vol. 16, no. 2, p. 266. <http://doi.org/10.3390/s16020266>.

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<http://dx.doi.org/10.19173/irrodl.v18i1.2621>

4. **García-Betances, Rebeca I.**, María Fernanda Cabrera-Umpiérrez, and María T. Arredondo. (2017). Computerized Neurocognitive Interventions in the Context of the Brain Training Controversy. *Reviews in the Neurosciences*, Published online 2017-08-19 ahead of print. <https://doi.org/10.1515/revneuro-2017-0031>

Impact Factor (2016): 2.546; Q3 in Neurosciences.

Other Scientific Publications

During the course of her doctoral studies other scientific articles co-authored by the candidate were published in journals or presented in specialized conferences related to topics of Ambient Assisted Living, Mild Dementia, and Health-care. They are:

1. Colomer, J.B.M., Salvi, D., Cabrera-Umpierrez, M.F., Arredondo, M.T., Abril, P., Jimenez-Mixco, V., **García-Betances, R.**, Fioravanti, A., Pastorino, M., Cancela, J. and Medrano, A. (2014). Experience in evaluating AAL solutions in living labs. *Sensors*, 14(4), pp.7277-7311. <http://dx.doi.org/10.3390/s140407277>.

Impact Factor (2014): 2.245; Q1 in Instruments & Instrumentation.

- 1.1. Kanstrup, Anne Marie. "Living in the lab: an analysis of the work in eight living laboratories set up in care homes for technology innovation." *CoDesign* vol. 13, n° 1 (2017): 49-64.
<http://dx.doi.org/10.1080/15710882.2016.1146304>
- 1.2. Pflügler, Johannes, et al. "Using Human-Computer Interface for Rehabilitation of Activities of Daily Living (ADL) in Stroke Patients: Lessons from the First Prototype." *Replace, Repair, Restore, Relieve—Bridging Clinical and Engineering Solutions in Neurorehabilitation*. Springer, Cham, (2014):629-636. http://dx.doi.org/10.1007/978-3-319-08072-7_90
- 1.3. Serral, Estefanía, et al. "Contextual Requirements Prioritization and Its Application to Smart Homes." *European Conference on Ambient Intelligence*. Springer, Cham (2017). http://dx.doi.org/10.1007/978-3-319-56997-0_7
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3. Quintana, M., Frögren, J., Stefan, M., Barnestein-Fonseca, P., Lemmens, E., **García-Betances, R. I.**, Seeman, L., and SMART4MD-Group. (2017). User-centred design adaptation smart4md: consulting people with dementia, carers and professionals. Presentation at the *6th Scientific Conference of the Federation of the European Societies of Neuropsychology (FESN)* in Maastricht, the Netherlands (13–15 September 2017).
4. **García-Betances R.I.**, Cabrera-Umpiérrez M.F., Colomer J.B.M., Castrillo M.P., Mata J.C., Arredondo M.T. (2017) Smart Assistive Technologies to Enhance Well-Being of Elderly People and Promote Inclusive Communities. In: Mokhtari M., Abdulrazak B., Aloulou H. (eds) Enhanced Quality of Life and Smart Living. ICOST 2017. pp. 3-12. *Lecture Notes in Computer Science*, vol. 10461. Springer, Cham. https://doi.org/10.1007/978-3-319-66188-9_1

APPENDIX B

ABRIDGED RESUME

of Rebeca Isabel García Betances

31 August 2017

PERSONAL INFORMATION:

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ACADEMIC INFORMATION:

PhD: Biomedical Engineering, Universidad Politécnica de Madrid.

Madrid, Spain. September 2013 – present.

Master's: Biomedical Engineering, Simón Bolívar University.

Caracas, Venezuela.

Degree: Magister in Biomedical Engineering (with Honors), December 2011.

“Uso de códigos gráficos 2D para identificación y acceso a datos de pacientes en centros de salud” Rebeca I. García Betances, Master's Thesis, Biomedical Engineering Graduate Program, Simón Bolívar University, published October 2011. <http://159.90.80.55/tesis/000152110.pdf>.

Undergraduate Education, Andrés Bello Catholic University.

Caracas, Venezuela.

Degree: Professional Engineer in Telecommunications, June 2009. Degree officially recognized as a Spanish university degree in Telecommunication Engineering, October 2012.

“Diseño de una red para aplicaciones de telemedicina la zona Baruta – El Hatillo” Rebeca García, Lorena Gilbert, Final Project Report, School of Telecommunications Engineering, Andrés Bello Catholic University, Caracas, Venezuela., February 2009.

OTHER COURSES:

- Gamification. The University of Pennsylvania's online course. March, 2015.

- “Desarrollo de Aplicaciones de Realidad Virtual con Worldviz Vizard en Entornos de Investigación”, Smart House Living Lab, UPM, Madrid Spain, March, 2013.

SCIENTIFIC PUBLICATIONS:

A total of 18 scientific publications. A complete list can be found at:
<https://scholar.google.es/citations?hl=en&user=goL6-qsAAAAJ>

WORK EXPERIENCE:

Senior Researcher, September 2012 – present

“LifeSTech: Life Supporting Technologies Group”

Universidad Politécnica de Madrid, Madrid, Spain.

<http://www.lst.tfo.upm.es/es/>

- Research activities in the areas of e-health, accessibility, e-inclusion, Ambient Assisted Living (AAL), and Virtual Reality.
- Participation in several proposal preparation of EU funded projects.
- Project Manager and team member of EU projects: PLAN4ACT (H2020-FETPROACT-2016- 732266), ACROSSING (H2020-MSCA-ITN-2015-676157) and SMART4MD (H2020-PHC-2014-643399).

Graduate Research Assistant, September 2009 – September 2011

“GRETA: Grupo de Redes y Telemática Aplicada” (Networks and Applied Telematics Group),

Simón Bolívar University, Caracas, Venezuela.

<http://greta.labc.usb.ve/>

- Development of patient identification and access to health records applications.

Undergraduate Research Assistant, February 2008 – February 2009.

“GBBA: Grupo de Bioingeniería y Biofísica Aplicada” (Bioengineering and Applied Biophysics Group), Simón Bolívar University, Caracas, Venezuela.

<http://www.gbba.usb.ve/>

- Design of Rural Telemedicine Wireless Networks.

Internship, July 2008 – September 2008.

School of Telecommunications Engineering,
Andrés Bello Catholic University, Caracas, Venezuela.

- Design of a Campus-wide Emergency Radio Network.

OTHER ACTIVITIES:

Academic Committee Member, September 2007 - May 2008.

“IV Jornadas de Ingeniería de Telecomunicaciones” and “III Encuentro Nacional de Estudiantes de Telecomunicaciones”, Caracas, Venezuela, May 2008.

Member of the Technical Program Committee, October 14, 2016.

First Ecuador IEEE Technical Chapters Meeting (ETCM 2016)
Guayaquil, Ecuador.

HONORS AND DISTINCTIONS:

Graduate Education:

1. Outstanding Mention: Master’s Thesis, October 2011.
2. Master’s Degree conferred with Honors, December 2011.