

Using Virtual Reality for Cognitive Training of the Elderly

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Rebeca I. García-Betances, MBE¹, Viveca Jiménez-Mixco, MTE¹,
María T. Arredondo, PhD¹, and María F. Cabrera-Umpiérrez, PhD¹

Abstract

There is a pressing demand for improving the quality and efficacy of health care and social support services needed by the world's growing elderly population, especially by those affected by mild cognitive impairment (MCI) and Alzheimer's disease (AD)-type early-stage dementia. Meeting that demand can significantly benefit from the deployment of innovative, computer-based applications capable of addressing specific needs, particularly in the area of cognitive impairment mitigation and rehabilitation. In that context, we present here our perspective viewpoint on the use of virtual reality (VR) tools for cognitive rehabilitation training, intended to assist medical personnel, health care workers, and other caregivers in improving the quality of daily life activities of people with MCI and AD. We discuss some effective design criteria and developmental strategies and suggest some possibly useful protocols and procedures. The particular innovative supportive advantages offered by the immersive interactive characteristics inherent to VR technology are discussed.

Keywords

virtual reality, cognitive rehabilitation, Alzheimer's disease, mild cognitive impairment

Introduction

As life expectancy continues to increase, the number of older people unable to live independently and in need of assistance because of cognitive impairments is rapidly rising worldwide.¹ The world's population aged older than 60 years is estimated to grow to about 2 billion by the year 2050.² Such circumstances entail severe social consequences regarding growing family burdens, lesser quality of life (QoL) and well-being, increasing health care demand, longer term utilization of care facilities, and so on, all of which generate very significant impacts on health care services demand and costs.^{1,3}

Memory impairment is one of the main cognitive issues that contribute to inability to live independently.^{1,4-6} Memory impairment in the early stages of dementia limits memory processes and reduces older people's autonomy when performing more complex daily activities. It concurrently causes deterioration of emotional control, social behavior, and motivation.^{2,3,6} 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 2050.⁷ Accordingly, the WHO recommends that dementia should be regarded and handled as a major public health issue because of its widespread high incidence.² Dementia disease represents one of the major challenges for health and

social services in Europe today.³ 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 they are expected to continue to rapidly increase.² 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.⁸

Additionally, prevalence of mild cognitive impairment (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.^{1,9,10} About 10% to 55% of cases with MCI turn into dementia over a 2- to 6-year period.^{1,2} Therefore, MCI can act as a predictor of dementia disease.^{1,6,11}

There is a growing social demand to significantly improve the quantitative and qualitative efficiency of health care and

¹Life Supporting Technologies (LifeSTech), Escuela Técnica Superior de Ingenieros de Telecomunicación, Universidad Politécnica de Madrid, Madrid, Spain

Corresponding Author:

Rebeca I. García-Betances, MBE, Life Supporting Technologies (LifeSTech), Escuela Técnica Superior de Ingenieros de Telecomunicación, Universidad Politécnica de Madrid, Avenida Complutense n° 30, Ciudad Universitaria, Madrid 28040, Spain. Email: rgarcia@lst.tfo.upm.es

social support services provision to the general population. 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 mitigation and rehabilitation can considerably contribute to address this problem. Emerging ICT applications based on virtual reality (VR) environments, including such novel means as Augmented Reality technology, can become important game changers.

In recent years, researchers have started to focus their attention on the prevention and treatment aspects of dementia.^{3,12,13,14} 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 behavioral interventions,⁸ for memory difficulties have gained much attention in recent years.⁵ Theories of brain plasticity mechanisms (ie, axonal sprouting, glial cell activation, denervation supersensitivity, 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.^{5,15} 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 behavioral symptoms such as depression, apathy, wandering, sleep disturbances, agitation, and aggression.⁸ There is evidence that some specific nonpharmacological therapies may improve or stabilize cognitive function in the performance of daily activities.¹⁶

Since there is still insufficient knowledge and experience on the use of VR environments to cognitive rehabilitation (CR) training for the treatment of MCI and patients with early dementia, strengthening research activities offers the possibility of ascertaining the potential efficacy of this technology as a useful tool in CR. 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.

Strategies for CR

Cognitive rehabilitation can be attempted by way of 2 main schemes known as the Restorative and Functional approaches.¹⁵ The former uses systematic cognitive processes that aim to retrain people on how to plan and conceive behaviors. The latter approach aims to functionally teach people to perform observable behaviors of daily living activities. Such interventions should be applied during the first stages of AD and could be applied also to patients with symptoms of MCI. Personal context is a foremost factor to identify effective cognitive interventions to reduce the progression of dementia. The design of appropriate CR training techniques to improve everyday memory to accomplish real-world tasks and daily functioning must emphasize the patient's personal context.¹

Studies have substantiated the effectiveness of brain plasticity theories and cortical activation in psychological aging CR.^{4,5} Functional neuroimaging yields evidence that certain cortical areas of older adults display greater or lesser activity depending on the task performed and conditions to which they are exposed.^{4,10,17,18} Cognitive training based on this brain plasticity concept has been found to improve cognitive functions that can last for up to 5 years after the intervention.⁵ Recent studies have also confirmed such improvements through the use of computerized cognitive training programs, offering further evidence of the beneficial effects of CR on memory and attention.^{19,20}

In spite of the fact that MCI and early-stage dementia represent key periods for providing effective patient intervention, CR is not being routinely offered for such patients.^{10,21} On the other hand, most of today's CR interventions in AD are mainly only focused on episodic memory intervention. There are several studies that confirm the efficacy of CR techniques in training individuals with MCI and dementia to learn, relearn, keep over time, and apply information to everyday contexts. Cognitive rehabilitation also helps to develop strategies to compensate for memory impairment and to adjust the environment to reduce memory demands.¹ There is also evidence of the efficacy of teaching visual or semantic mnemonics to improve episodic memory in individuals with early-stage dementia.^{10,22} Analytic reviews of cognitive training indicate that techniques such as Errorless Learning and Spaced Retrieval are promising procedures for memory training in patients with AD.^{5,23} The potential usefulness of noninvasive nonpharmacological CR intervention in the early stages of AD has been already accredited by various studies reported in the specialized literature.^{5,24}

Computers in Neuropsychology

The use of computers in psychological testing began over a quarter of a century ago.²⁵ Today 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.²⁴ 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.²⁶ Several fields, such as Domotics, Ambient Intelligence (AmI), e-services, and telemedicine, are examples of this trend.

A few computer-based CR exploratory programs have been carried out aimed at elderly people who have dementia.^{19,24} There are also several projects and research studies developed in the last 2 decades where computer-based interventions were suggested for memory training and CR of elderly people with MCI and early-stage dementia. Such incipient training intervention actions already reveal the potential benefits to function improvement in select cognitive tasks such as face-name association, memory, attention, list recall, and so on.^{9,24}

Virtual Reality in CR

Virtual reality is a novel branch of ICT that has been suggested recently for use in the area of neuropsychology. Virtual reality is founded on several perception components of psychophysics, the foremost of which are visual, tactile, and kinesthetic perceptual sensations. The use of VR systems offers the possibility of simulating immersive and interactive real-life scenarios to produce a sensation of “being there.” Virtual reality also offers the ability to perform tests in an adaptive environment that can be adjusted according to various patients’ needs.^{25,27} The use of VR systems for disease treatment has been already explored in several areas, such as brain damage, poststroke intervention, musculoskeletal recovery, and so on.^{28,29} Immersive VR environments have also been used for neuropsychological assessment and CR therapies such as phobias, stress, anxiety, exercise, and memory problems.^{27,28,30-36}

The potential of VR and of virtual environments (VEs) is presently being investigated by several research groups and laboratories, focusing on cognitive processes, including attention, executive functions, memory,²⁷ motor rehabilitation,²⁸ special abilities,³⁷ and spatial orientation.³⁸ Virtual reality scenarios have been also designed for testing instrumental activities of daily living, including wheel chair navigation.³¹ Some VR systems and applications for patients with MCI and dementia have been developed in recent years. However, still there seems to be insufficient unambiguous evidence of the benefits of use of VR systems for CR of patients with MCI and dementia.³⁰ Some feasibility studies done on the use of this type of systems with such patients did not provide evidence of significant improvements, and rather point out instances of VE simulator acceptance problems.³⁹ On the other hand, there are differing reports, which indicate that patients feel a sense of control and enjoyment while interacting with the VE.³⁹ Still other researchers concur in recognizing the benefits of using suitable VE for CR of patients with early-stage dementia.^{15,35} Virtual reality systems and applications seek to address various diverse treatments for patients with MCI and dementia, such as navigation and orientation,^{2,15,35,40} face recognition,⁴¹ cognitive functioning^{27,35,37,40} as well as other instrumental activities of daily living.^{23,42,43}

It is therefore evident that the regular use of VR-based training technology for MCI and dementia rehabilitation still requires broader and deeper study and research. The development of adaptable, friendly, and easy to interact with VEs, especially tailored for cognitive training of patients with MCI and dementia, is a must to facilitate further research in this field and to be able to implement viable CR processes to maximize its effectiveness. Well-designed and soundly described clinical protocols, properly controlled trials, and long-term follow-ups are indispensable to reach solid conclusions about the efficacy of use of VR systems in rehabilitation of patients with MCI and dementia.^{15,34}

Virtual reality-Based CR Training

In the general context described previously, the use of VR technology in CR constitutes a valuable tool to better meet the

impending challenges posed by the need to qualitatively and quantitatively improve elderly patients’, their families’, and their caregivers’ overall QoL. Additionally, VR-based CR systems can become much needed systematic CR test platforms, as well as effective sources of reliable information, for age-related cognitive impairment specialists. The implementation of VR-based CR systems opens up enormous possibilities for innovation beyond the state of the art in several operational aspects of CR, some of which are mentioned subsequently:

- Active involvement of specialists, caregivers, and users in the interdisciplinary process of designing and developing a VR system specifically for CR, in correspondence to their circumstances, unique needs, and appropriate customized training protocols.
- Availability of advanced, adaptable, and easy-to-use multisensory VR platform interfaces where strategies and procedures for patients’ interaction and navigation tasks can be developed and tested.
- Attainment of true immersive presence so that patients may be treated physically inside a VE.
- Convergence of diverse behavioral, cognitive, and experimental scientific and technological means and approaches into a multidisciplinary integrated setting.
- Accessibility to a high level of experimental control, allowing the study of diverse brain-stimulation activities within different areas: memory, attention, language, executive functions, and functional activities of daily living, and so on.
- Researchers’ and specialists’ access to real-time feedback and data collection capacity, to gather performance information during the course of the CR training activities, to be used for analysis of patients’ rehabilitation evolution and procedure effectiveness evaluation and tuning.
- Systematic production of robust facts and statistics about the effectiveness of VR-based CR therapies for patients with MCI and early-stage AD that can be a source of reliable information for further research.

Key Objectives and Developmental Methodologies

Developing, designing, implementing, and optimizing VR-based CR training tools to help mitigate cognitive, behavioral, and psychological impairment symptoms of the elderly population is the fundamental objective. Any implemented platform should also provide useful support and timely information to assist clinicians and caregivers to improve the QoL of elderly people affected by MCI and early-stage AD dementia.

The design and development of CR training activities in the framework of VR technology must be carried out within the following domains: memory, attention, language, executive functions, and functional activities of daily living. The design result should be a VR training system that is easy to use by this type

of patients and that is capable of providing effective feedback of the progress of their rehabilitation. The goal is that the VR-based CR system becomes an instrument for tuning CR procedures as well as a useful tool for further research and development.

The VR-based CR platform ought to be decisively multidisciplinary, in that it should facilitate joint work among researchers, technical and medical specialists, and caregivers, aimed at attaining an interdisciplinary development of strategies and procedures to fulfill the patient's specific rehabilitation needs as well as the caregivers' intervention requirements.

The VR-based CR system's working approach needs to be itself multidisciplinary in nature, in the sense that it should empower cross-enrichment among diverse scientific and technological disciplines such as computer-based QoL technologies, ICTs, VR, e-health technologies, human-computer interfaces, biosensor systems and technologies, cognitive science, sensory perception psychophysics, neuropsychology, noninvasive treatment, training strategies, and so on.

There are some specific working objectives that in our judgment are most relevant for chronologically guiding the successful development of VR-based CR systems to mitigate age-related cognitive impairments. They may be separated into scientific and technological categories and briefly enunciated as follows:

Scientific

- S1. Analysis of existing MCI and early-stage AD cognitive models.
- S2. Identification of theories, methods, and activities currently in use by specialists who are treating CR issues in patients with MCI and early-stage AD.
- S3. Study of the potential acceptance and identification of technological barriers that the use of VR might present to patients with MCI and early-stage AD.
- S4. Definition of patients', specialists', and caregivers' needs, in order to effectively address them in the context of the VR-based CR training system.
- S5. Critical analysis of results on the basis of data collected from patients' CR pilot trials.

Technological

- T1. Description, specification, and design of the system, considering patients' needs, acceptance, and technological barriers, and taking into account specialists' and caregivers' requirements.
- T2. Development of VR platform simulation environments, on the basis of cognition rehabilitation training methods and activities previously agreed upon with specialists.
- T3. Simulations of system design to be implemented in the VR facility in order to test correct performance according to specifications.
- T4. Validation by specialists of the system's design through pilot trials.

To assure that the design methodology is firmly founded on a comprehensive multidisciplinary approach, it is convenient that it be carried out systematically, preferably distributed among specific methodological phases, as described subsequently.

Phase 1

The first phase involves all the preliminary research and data collection referred to the end users (patients, specialists, and caregivers). This phase aims to achieve scientific objectives S1 to S5 by first conducting research reviews and analysis of specialized literature, followed by polling surveys and personal interviews and questionnaires, in order to identify and define patients' cognitive models and profiles, professional users' needs as well as possible technological and acceptance barriers specifically related to the use of VR systems.

Phase 2

This second phase deals with the interdisciplinary nature of the design and development of the VR system itself. It should accomplish technological objectives T1 to T3, which involve the selection of the CR methods and activities to be used in the design, all based on the information collected during the first phase. System components and requirements are defined at this stage. Data gathering capabilities are integrated into the simulation environment in this phase, to allow the collection of patients' performance data during the course of the CR training activities. System testing and VR environment simulation are also carried out to confirm operation according to specifications.

Phase 3

This phase's purpose is to assess system design and analyze its efficacy. Scientific objective 5 and technological objective 4 should be fulfilled, through pilot trial testing of the VR-based CR training system, applying CR therapy procedures to controlled groups of patients with MCI and early-stage AD, over a period of time. Data collected by the system about patients' accomplishments and evolution should be used, together with medical and technical specialists' evaluations, to ultimately complete critical multidisciplinary analysis of the effectiveness of the VR-based CR training system and its therapeutic procedures, including meaningful conclusions and useful recommendations.

Discussion

The European Union decided in 2011 to encourage, assist, and support the improvement in dementia prevention, diagnosis, treatment, and patient care. The research, development, and implementation of VR-based training systems for cognitive impairment mitigation and rehabilitation of people affected by age-related cognitive impairments directly addresses several important elements of the European Parliament resolution about the European initiative on AD and other dementias.⁴⁴ Specifically, the use of VR-based CR training systems would:

- offer effective support to patients with MCI and early-stage AD and caregivers to enhance the QoL of these patients in their familiar environment;
- place a particular focus on appropriate therapeutic interventions for the predementia 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
- introduce novel multidisciplinary approaches to foster the syntrophic enrichment of knowledge for MCI and early-stage AD prevention, diagnosis, treatment, and care giving.

Motivated by this European initiative, we have begun work at Life Supporting Technologies (LifeSTech) in this field of VR-based CR training by means of a currently underway project entitled “Cognitive Training through Virtual reality for the Elderly (aCTIVATE).” This project utilizes the Smart House Living Lab’s VR facilities at LifeSTech in the Telecommunications Engineering School of Universidad Politécnica de Madrid (UPM).⁴⁵ Its main objective is to develop, design, and optimize VR-based CR training tools for mitigating cognitive, behavioral, and psychological impairment symptoms. It intends to provide useful support and timely information to assist health workers, caregivers, and clinicians to improve the QoL of elderly people affected by MCI and early-stage AD dementia. The contributions of this project will be in the form of R&D + i advancements regarding new VR-based methods, approaches, and technologies to help advance CR solutions for cognitive impairment mitigation in the aging population. The goal is that it becomes an instrument for tuning CR procedures as well as a useful tool for further research and development.

Conclusion

Virtual reality-based CR systems are capable of achieving the expected training goals for people affected by age-related cognitive impairments. They support procedures for mitigating behavioral and psychological symptoms of patients having MCI and early-stage AD, to best fulfill these patients’ specific rehabilitation needs, as well as their caregivers intervention requirements.

In addition to the overall relevance of the contributions to the current state of the art of CR, a salient feature of implementing VR-based CR training systems is the reliance on intense multidisciplinary collaboration during the innovation and system design phases as well as the high level of involvement on the part of patients, physicians researchers, technical specialists, and caregivers.

A more comprehensive and far-reaching aspect of developmental VR-based CR training systems is that they also become versatile experimental platforms that can provide timely information and useful feedback to clinicians and caregivers through continuous monitoring of system performance. Such systematic information is the basis for producing significant contributions to the strategic “active and healthy aging” QoL undertakings as well as to other ambient intelligence endeavors in general.

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References

1. Seelye A, Schmitter-Edgecombe M, Das B, Cook D. Application of cognitive rehabilitation theory to the development of smart prompting technologies. *IEEE Rev Biomed Eng.* 2012;5:29-44.
2. World Health Organization. Dementia: A public health priority. 2012. http://whqlibdoc.who.int/publications/2012/9789241564458_eng.pdf. Accessed February 08, 2014.
3. Monteagudo J. Capacidades y Oportunidades de Innovación en TIC para Alzheimer. Unidad de Investigación en Telemedicina, Instituto de Salud Carlos III. Madrid, Spain, 2012. <http://publicaciones.isciii.es>. Accessed February 08, 2014.
4. Grady C, Craik F. Changes in memory processing with age. *Curr Opin Neurobiol.* 2000;10(2):224-231.
5. Cotelli M, Manenti R, Zanetti O, Miniussi C. Non-pharmacological intervention for memory decline. *Front Hum Neurosci.* 2012;6:46
6. Schmitter Edgecombe M, Woo E. Characterizing multiple memory deficits and their relation to everyday functioning in individuals with mild cognitive impairment. *Neuropsychology.* 2009;23(2):168-177.
7. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement.* 2013;9(1):63-75.
8. Alzheimer’s Association Report. 2013 Alzheimer’s disease facts and figures. *Alzheimers Dement.* 2013;9(2):208-245.
9. Belleville S, Gilbert B, Fontaine F, Gagnon L, Ménard E, Gauthier S. Improvement of episodic memory in persons with mild cognitive impairment and healthy older adults: evidence from a cognitive intervention program. *Dement Geriatr Cogn Disord.* 2006;22(5-6):486-499.
10. Thivierge S, Simard M, Jean L, Grandmaison E. Errorless learning and spaced retrieval techniques to relearn instrumental activities of daily living in mild Alzheimer’s disease: a case report study. *Neuropsych Dis Treat.* 2008;4:987-99. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2626924/>. Accessed February 02, 2014.
11. Farias S, Mungas D, Bruce R, Harvey D, Cahn-Weiner D, DeCarli C. MCI is associated with deficits in everyday functioning. *Alzheimer Dis Assoc Disord.* 2006;20(4):217-223. <http://www.ncbi.nlm.nih.gov/pubmed/17132965>. Accessed February 02, 2014.
12. Borson S, Frank L, Bayley P, et al. Improving dementia care: the role of screening and detection of cognitive impairment. *Alzheimers Dement.* 2013;9(2):151-159.
13. Cordell CB, Borson S, Boustani M, et al. Alzheimer’s Association recommendations for operationalizing the detection of cognitive

- impairment during the medicare annual wellness visit in a primary care setting. *Alzheimers Dement*. 2013;9(2):141-150.
14. Clare L, Bayer A, Burns A, et al. Goal-oriented cognitive rehabilitation in early-stage dementia: study protocol for a multi-centre single-blind randomized controlled trial (GREAT). *Trials*. 2013; 14:152. <http://www.trialsjournal.com/content/14/1/152>. Accessed February 02, 2014.
 15. Morganti F. Virtual interaction in cognitive neuropsychology. *Stud Health Technol Inform*. 2006;99:55-70. <http://www.ncbi.nlm.nih.gov/pubmed/15295146>. Accessed February 02, 2014.
 16. Olazarán J, Reisberg B, Clare L, et al. Nonpharmacological therapies in Alzheimer's disease: a systematic review of efficacy. *Dement Geriatr Cogn Disord*. 2010;30(2):161-178.
 17. Buldú J, Bajo R, Maestú F, et al. Reorganization of functional networks in mild cognitive impairment. *PLoS One*. 2011;6(5): e19584.
 18. Celone KA, Calhoun VD, Dickerson BC, et al. Alterations in memory networks in mild cognitive impairment and alzheimer's disease: an independent component analysis. *J Neurosci*. 2006; 26(40):10222-10223.
 19. Smith G, Housen P, Yaffe K, et al. A cognitive training program based on principles of brain plasticity: results from the improvement in memory with plasticity-based adaptive cognitive training (IMPACT) study. *J Am Geriatr Soc*. 2009;57(4):594-603.
 20. Zelinski E, Spina L, Yaffe K, et al. Improvement in memory with plasticity-based adaptive cognitive training: results of the 3-month follow-up. *J Am Geriatr Soc*. 2011;59(2):258-265.
 21. Hampstead B, Sathian K, Moore A, Nalisnick C, Stringer A. Explicit memory training leads to improved memory for face-name pairs in patients with mild cognitive impairment: results of a pilot investigation. *J Inter Neuropsychol Soc*. 2008;14(5): 883-889.
 22. Rozzini L, Costardi D, Chilovi B, Franzoni S, Trabucchi M, Pado-vani A. Efficacy of cognitive rehabilitation in patients with mild cognitive impairment treated with cholinesterase inhibitors. *Int J Geriatr Psychiatry*. 2007;22(4):356-360. <http://www.ncbi.nlm.nih.gov/pubmed/17117398>. Accessed February 08, 2014.
 23. Belleville S, Clément F, Mellah S, Gilbert B, Fontain F, Gauthier S. Training-related brain plasticity in subjects at risk of developing Alzheimer's disease. *Brain*. 2011;134(pt 6):1623-1634.
 24. Cipriani G, Bianchetti A, Trabucchi M. Outcomes of a computer-based cognitive rehabilitation program on Alzheimer's disease patients compared with those on patients affected by mild cognitive impairment. *Arch Gerontol Geriatr*. 2006;43(3):327-335.
 25. Riva G. Virtual Reality as Assessment Tool in Psychology. *Virtual Reality in Neuro-Psycho-Physiology*. 1998; 44:71-79. <http://www.ncbi.nlm.nih.gov/pubmed/10175344>. Accessed February 08, 2014.
 26. Europe 2020. http://ec.europa.eu/europe2020/index_en.htm. Accessed February 08, 2014.
 27. Optale G, Urgesi C, Busato V, et al. Controlling memory impairment in elderly adults using virtual reality memory training: a randomized controlled pilot study. *Neurorehabil Neural Repair*. 2010;24(4):348-357.
 28. Tost D, Grau S, Ferre M, et al. PREVIRNEC: a cognitive telerehabilitation system based on virtual environments. *Virtual Rehabil Inter Conf*. June 29-July 2, 2009;87-93.
 29. Gervasi O, Magni R, Zampolini M. Nu! RehaVR: virtual reality in neuro tele-rehabilitation of patients with traumatic brain injury and stroke. *Virtual Reality*. 2010;14:131-141.
 30. García L, Kartolo A, Méthot-Curtis E. A discussion of the use of virtual reality in dementia. In: Dr. Christiane Eichenberg (Ed.). *Virtual reality in psychological, medical and pedagogical applications*. chapter 6. New York: InTech, 2012. ISBN: 978-953-51-0732-3.
 31. Rizzo A, Buckwalter JG, van der Zaag C, et al. Virtual environment applications in clinical neuropsychology. *Proc IEEE Virtual Reality Conf*. New Brunswick: NJ, March 18-22, 2000;63-70.
 32. Esteves R, Vidal L. The acceptance of virtual reality devices for cognitive rehabilitation: a report of positive results with schizophrenia. *Compt Methods Programs Biomed*. 2004;73(3):173-182.
 33. Riva G. Virtual Reality in Psychotherapy: Review. *Cyberpsychol Behav*. 2005;8(3):220-240. http://www.neurovr.org/pdf/papers/VR_Clinical/VR_in_psychotherapy.pdf. Accessed February 10, 2014.
 34. Gregg L, TARRIER N. Virtual Reality in mental health: a review of the literature. *Soc Psychiatry Psychiatr Epidemiol*. 2007;42(5): 343-354.
 35. Buss B. Virtual Reality Training System for Patients with Dementia. Master Thesis; September 2009. <http://e-collection.library.ethz.ch/eserv/eth:205/eth-205-01.pdf>. Accessed February 10, 2014.
 36. Virtualware Group. <http://virtualwaregroup.com/>. Accessed February 15, 2014.
 37. Parsons T, Rizzo A. Initial validation of a virtual environment for assessment of memory functioning: virtual reality cognitive performance assessment test. *CyberPsychol Behav*. 2008;11(1):17-25.
 38. Kober SE, Wood G, Hofer D, Kreuzig W, Kiefer M, Christa Neuper C. Virtual reality in neurologic rehabilitation of spatial disorientation. *J Neuroeng Rehabil*. 2013;10:17.
 39. Flynn D, van Schaik P, Blackman T, Femcott C, Hobbs B, Calderon C. Developing a virtual reality-based methodology for people with dementia: a feasibility study. *Cyberpsychol Behav*. 2003;6(6):591-611.
 40. Cushman L, Duffy C. Detecting navigational deficits in cognitive aging and Alzheimer disease using virtual reality. *Neurology*. 2008;71(12):888-895.
 41. Boggio P, Valasek CA, Campanha C, et al. Non-invasive brain stimulation to assess and modulate neuroplasticity in Alzheimer's disease. *Neuropsychological Rehab*. 2011;21(5):703-716.
 42. Lee JH, Ku J, Cho W, et al. A Virtual reality system for the assessment and rehabilitation of the activities of daily living. *CyberPsychol Behav*. 2003;6(4):383.
 43. Imbeault F, Bouchard B, Bouzouane A. Serious Games in Cognitive Training for Alzheimer's Patients. *IEEE 1st Inter Conf Serious Games and Applicat for Health (SeGAH)*, Braga: IEEE, 2011.
 44. European Parliament. European initiative on Alzheimer's disease and other dementias. 2010. Available in: <http://www.europarl.europa.eu/sides/getDoc.do?type=REPORT&reference=A7-2010-0366&format=XML&language=EN>. Accessed February 08, 2014.
 45. Advanced Multimodal room for Interaction in Virtual Reality, Smart House Living Lab. ETSIT, Universidad Politécnica de Madrid (UPM), Moncloa Campus of International Excellence, Madrid, Spain. Available in: <http://www.lst.tfo.upm.es/es/research-areas/smart-infrastructure/smart-house-living-lab/>. Accessed February 10, 2014.