Aging, Cognitive Rehabilitation and eHealth: Insights from Clinical Neurosciences to Neuropsychology in Portugal

Envelhecimento, Reabilitação Cognitiva e E-Saúde: Dados das Neurociências Clínicas na Intervenção em Neuropsicologia em Portugal

André Carvalho[1]*, *Marta Moreno*[2]

*** Corresponding Author/**Autor Correspondente:
André Miguel Alves de Carvalho [andre.alves.carvalho@lusiadas.pt].
R. Abílio Mendes 22, 1500-473 Lisboa, Portugal

Abstract

Data from different sources indicate that the number of people with cognitive problems, dementia and psychopathology is increasing due to population ageing. The aging process in Portugal also has particular characteristics in the population due to vascular risk factors and other psychosocial comorbidities that can affect the quality of life of the elderly. Holistic cognitive intervention has shown good results in the prevention and rehabilitation of neurocognitive diseases using eHealth and different technologies in mental health, based on the neuroanatomical and functional knowledge of the brain at the level of neuronal connectivity; cognitive reserve and synaptic plasticity. But working with the geriatric population can be a great challenge for clinical neuropsychology since the frontier between healthy and pathological aging can be difficult to define. And for this reason, it is increasingly important to develop diagnostic and intervention methods adapted to the modern lifestyle with a balanced cost-effectiveness ratio accessible to the general population in cognitive rehabilitation programs.

Keywords: Aging; Cognition; Health Status; Rehabilitation

Resumo

Dados de diferentes estudos indicam que o número de pacientes adultos com doenças da cognição tal como a demência e psicopatologia associada, é cada vez mais frequente devido ao envelhecimento da população. O fenómeno em si do envelhecimento em Portugal apresenta características particulares na população devido a fatores de risco vascular e outras comorbidades psicossociais que podem afetar a qualidade de vida dos mais velhos. A intervenção cognitiva holística tem demonstrado bons resultados na prevenção e reabilitação de problemas neurocognitivos utilizando diferentes tecnologias de informação e comunicação em saúde mental e E-Saúde, baseadas no conhecimento neuroanatómico e funcional do cérebro ao nível da sua conectividade neuronal; reserva cognitiva e plasticidade sináptica. Mas trabalhar com a população geriátrica em neuropsicologia clínica pode ser um grande desafio uma vez que a fronteira entre o envelhecimento saudável e patológico pode ser difícil de definir. Por isso é cada vez mais importante desenvolver metodologias de diagnóstico e de intervenção adaptadas ao estilo de vida atual em Portugal desta população, sem perder de vista o acesso à melhor relação custo-efetividade possível em saúde no tratamento em reabilitação cognitiva.

Palavras-chave: Cognição; Envelhecimento; Nível de Saúde; Reabilitação

1. Especialidade de Neuropsicologia, Grupo Lusíadas Saúde Lisboa, Portugal; Assistente no Departamento de Saúde Mental do Hospital Prof. Dr. Fernando-Fonseca, Amadora, Portugal. **2.** Diretora Clínica do European Aviation Wellbeing Committee, Dublin, Irlanda.
Received/Recebido: 05/02/2021 - **Accepted/Aceite:** 11/02/2021 - **Published/Publicado:** 31/03/2021

Introduction

Portugal is the 4th country in the European Union with the highest percentage of older people surpassed only by Greece, Germany and Italy. In 2015 life expectancy at birth was 77.4 years for men, while for women it was 83.2 years.[1] The increase in average life expectancy and age are risk factors for cognitive aging[2-4] and dementia in the elderly.[5]

Psychopathology is also present in aging mental changes, such as anxiety, depression and insomnia.[6] People with post-traumatic stress disorder are more likely than others to develop dementia later in life, according to a research from The British Journal of Psychiatric. It consists on a meta-analysis of 13 longitudinal studies that surveyed a total of 1 693 678 participants for as long as 17 years.[7] Substance abuse such as alcohol[8]; complicated mourning situations[9] and psychotic disorders including schizophrenia and delusional disorders[10] are also found in this age range. In Portugal, depression has a prevalence of 7.5% in women between 55-74 years of age[11] and, in 2014, suicide rate per 100 000 inhabitants, was of 21.6%, in individuals with age equal to 65 and more than 25.6% in individuals over 70.[12]

In any case, the epidemiological perspectives show a progressive increase in the number of cognitive decline and dementia cases in Portugal.[13-16] The incidence of cognitive impairment is 12.3% and 2.7% for dementia between 55 and 79 years old, becoming higher in elders.[17] The most common causes of (degenerative) dementia are Alzheimer's disease[18,19] and other dementia subtypes, such as vascular dementia,[20] frontotemporal dementia[21] and dementia with Lewy bodies.[22]

Aging can also be relatively healthy associated with a cognitive decline not severe enough to condition functional capacity in activities of daily routine. In these cases, and based on a neuropsychological assessment, a mild cognitive impairment of different subtypes (e.g. amnestic versus non-amnestic domains; single versus multiple) can be diagnosed and progressive neurocognitive symptoms can be early prevented.[23] There are also treatable biological causes of cognitive impairment and reversible dementia (e.g. drug toxicity; thyroid dysfunction, vitamin B12 deficiency; inflammatory or systemic diseases.[24] Another aspect that has an impact on physical well-being and mental health is the prevention of cardiovascular diseases and associated risk factors that can impair cognitive functioning.[25,26]

High blood pressure, diabetes, smoking and obesity have been associated with unhealthy aging and an increased risk of neurodegenerative diseases such as Alzheimer's disease.[27]

But in general, there can be a substantial heterogeneity in the trajectories of cognitive aging, with some individuals showing minimal or no decline.[28,29] Therefore, discovery of sensitive, specific and non-invasive biomarkers is a prerequisite for identifying high-risk individuals, and developing effective strategies that can monitor, delay or prevent the onset of neurocognitive and aging mental disorders.

I. Brain function and relevant historical data

Current views on brain-behavior relationships stem from the merger in the late 19th century of neuroanatomy; neurophysiology; neurochemistry and cognitive psychology.

It is possible that our ancestors already linked the functions of the head with the maintenance of life. Stanley Finger (2019)[30] describes a fractured *Australopithecus Africanus* skull that is said to have been the target of aggression in a death match between enemy groups. James Breasted, an Egyptologist at the University of Chicago, translated in 1930 a famous surgical papyrus from Egypt where there were original references to lesions of the cerebral hemispheres described by Imhotep, a doctor who accompanied the Egyptian armies in their battles around 2500 BC. In the 5th century BC, from Alcmaeon's descriptions, there was the idea that visual perception was kept in the brain through the optic nerve and that the eyeball was filled with liquid up to the cavities of the three ventricles. Theory was accepted by Descartes in the 17th century, proposing another physiological model in which the "thirst of the soul" was located in brain structures such as the epiphysis. The ventricular theory remained until the Renaissance period when new representations of anatomy resulted from the explosion of pictorial art, namely, with the illustrative drawings of the brain by Leonardo Da Vinci.

In 1976 with the work of Franz Joseph Gall,[30] an Austrian doctor, a new theory called Phrenology developed in Europe. Based on this theory, it was not only the ventricles that were the important part of the brain, but also its own structure that had organs capable of performing functions and that shaped the skull cap. Through a thorough analysis of the head configuration, it was possible to predict the psychological and personality skills of a certain individual.

Based on the theoretical assumptions of phrenology Paul Broca, currently recognized as the father of cerebral dominance, worked in 1825 with Bouillaud to create a new experimental model, based on the study of patients with localized brain injuries. The hypothesis was that "if a particular phrenological organ were injured, the function for which it was responsible was lost". The first patient studied was called Leborgne and had oral language restricted to the word *tan*. After having studied several patients with identical symptoms and brain injuries in the left hemisphere, Broca stated in 1865 that the articulated language was located in the third frontal circumvolution of the left hemisphere.

Another famous case related to the frontal lobe's brain functions is that of Phineas Gage in 1868 who was a young construction worker in the United States of America who was the victim of a serious accident, during which a sharp punctured him from the lower jaw to the skull.[31] Gage survived the trauma without motor sequelae, but his personality trait changed

profoundly in social conduct, becoming unstable, impulsive and conflictive. Friends no longer recognized him as the same person considering that "Gage was no longer Gage". In this context, in Portugal, it is important to mention the remarkable scientific work of Egas Moniz with the prefrontal leukotomy that gave him a Nobel Prize in 1949, bringing new perspectives in the treatment of mental illnesses of the psychiatric sphere. In the middle of the 19th century and the beginning of the 20th century, the globalist current of thought arised with an evolutionary theoretical vision, introducing the notion of hierarchy between nerve centers, stipulating that higher "centers" would result from the combination of elementary functions, which implies conceiving the brain as a whole when considering a function. A series of mental functions based on the anatomy-clinical method were studied. This consists on observing an individual with a functional alteration related to a brain injury or dysfunction. Numerous neurological and neuropsychological syndromes were described.

Still in the 90s, the theory of the "somatic marker hypothesis" postulated by António Damásio (1996)[32] about the role of the orbitofrontal cortex in social adaptation, established that during our development we are creating somatic representations corresponding to the emotional manifestations felt in a given situation or context. Due to its connections with the limbic and hypothalamus systems, the fronto-orbital cortex would be the center of coupling and memorization of a given social context with a particular activity in the neurovegetative autonomic nervous system. In fact, we are endowed with a nervous system that allows our organism to react; interact and communicate with the outside. Therefore, we can admit that our individuality does not end in the activity of the central nervous system (CNS), it is more than that, because outside our consciousness we depend on functions of rapid regulation (eg. cardiovascular system) or slower regulation (eg. neuroendocrine system) to survive and adapt to the environment and its multiple diversities.

Currently, in the middle of the 21st century, with the technological development of neurosciences and the possibility of increasingly improved imaging and physiology techniques, there has been considerable progress in the knowledge of different brain regions and on the neurobiological substrate of several mental functions.

Neuromodulation and the nervous system as a whole

Almost all body functions are dependent on the autonomic nervous system (ANS), which exerts precise control over visceral functions. The ANS operates mainly through negative feedback mechanisms and via reflex arcs in order to restore the system homeostasis in case of an imbalance. It uses specific neuronal pathways that lead to an integrative autonomic network center located in the CNS to which sensory information is conveyed from peripheral sensors.[33,34] These autonomic reflex arcs are complex in nature due to the recruitment of rapid and synchronized sympathetic and parasympathetic activation across central and peripheral neuronal pathways.[35] It has the ability to influence and modulate the brain activity itself at the CNS level.

In this context, the principle of neuronal self-regulation refers to the cortical balance between the levels of excitability and synaptic inhibition, called neuromodulation[36] which, in turn, can also influence neurovisceral activity. Neuromodulation is based on the modulation of the general alertness level of the brain acting on the reticular activation system of the brain stem, which is part of the central autonomic network, responsible for regulating our level of consciousness and the wake-sleep cycle. In fact, our nervous system was designed millions of years ago to react automatically to emergencies in nature such as the imminent danger of attack by predators. This response is called sympathetic because it mobilizes us to action by pumping blood to the heart and muscles, by increasing the heart rate. Both *fight* and *flight* are immediate alert states designed for survival, which generate a great metabolic consumption and can inhibit other healthy physiological mechanisms of growth and repair, as it happens in mentally disturbed and anxious patients that feel a permanent sensation of danger and insecurity. On the other hand, the parasympathetic response attenuates the sympathetic tone by decreasing, for example, the heart rate, making the person more relaxed and with a feeling of greater control. In this state of relief, we conserve energy, improve the rhythm of the sleep-wake cycle and promote growth, which are fundamental conditions for well-being and development for a better mental recovery process.

Some studies have shown that the regulation of the sympathetic tone of the autonomic nervous system can optimize the signal of the brain circuits and thereby improve the quality of interaction and social ties.[36]

Neurostimulation and the importance of cognitive rehabilitation

Knowing that the brain works in an integrated way with our entire organism and that there is structural and functional connectivity[37] between different regions of the CNS, it is possible to better understand the concepts of cognitive reserve (CR) and neuroplasticity, fundamental in a therapeutic rehabilitation process.

The concept of CR has been developed in the past decades as a potential factor able to determine individual differences in cognitive vulnerability and trajectories occurring with aging.[38] Indeed, human aging is a complex and individualized

process which results from the interaction between multiple biopsychosocial factors. Different trajectories allow to distinguish healthy from pathological aging.[39] For this reason, CR has been defined in terms of "adaptability as a form of explaining differential susceptibility of cognitive abilities or day-to-day function of brain aging, pathology or insult"[40] and has a potential protective factor against the onset of negative age-related outcomes, including functional impairments and dementia.[41]

Individuals with higher education and CR should be able to tolerate more brain pathology before the onset of cognitive symptoms compared with those having lower CR. Education is one of the most widely accepted protective factors in the epidemiological studies of dementia.[42,43] And evidence derived from population-based studies has recently highlighted the beneficial impact of occupational status on cognitive aging, showing that carrying out complex jobs in adulthood is associated with reduced risk of dementia.[44] In this context, the potential role of leisure time activities in the prevention of cognitive decline and incident dementia in older people has also been debated[45] because an active and frequent social participation seems to result in an enhanced use of brain networks structure.[41,46] Less social participation and social interactions constitute significant risk factors for the development of cognitive dysfunction.[47]

Just like it happens with animals,[48,49] Eriksson and collaborators (1998)[50] established that even in humans throughout adult life, there are cells in the hippocampal formation capable of producing new neurons. There are neurogenic regions already identified, such as the subventricular zone that is located laterally to the cerebral ventricles and the subgranular zone of the dentate gyrus in the hippocampus. Therefore, enhancing the natural and spontaneous recovery of the brain through neurostimulation in attempt to restore lost functioning, combining non-pharmacological intervention with psychopharmacological treatment, can promote excitability in the formation of synaptic connections in neural networks not affected by the lesion, functionally recruiting neurons that would not normally be involved in that activity.[51] But the potential for rehabilitation due to a cerebral pathology also depends on its cause (e.g.: neurodegenerative, cerebrovascular or traumatic), the location and extent of the injury. Thus, the concept of neuroplasticity is defined as the ability of the nervous system to adapt and optimize its limited resources in response to physiological changes, injuries, new environmental demands and sensory experiences.[52] Thanks to our neuronal plasticity, as already mentioned, it is possible to reorganize an existing neuronal network by recruiting new areas for this circuit and promoting plasticity in regions that surround the injured area.

Cognitive rehabilitation (RCog) is a neurostimulation intervention model that has shown good results because it is a biopsychosocial approach with the aim of recovering (reorganizing) or compensating for cognitive deficits, improving a patient's daily functioning to a level higher than it would be achieved by the simple passage of time.[53] It is a holistic model of rehabilitation that intervenes on the neurocognitive changes (direct support) of the patient's environmental, social, family, emotional and motivational factors in a continuous treatment process, which can be remotely monitored from home (indirect support).

The concept of "rehabilitation" arose in 1918 out of society`s compassion for the mutilated veterans of World War I but it took a second destructive world conflict to prompt governments, notably in the U.S, to develop facilities and programs for the rehabilitation of the limbless, paralyzed, blind, deaf and "shell-shocked" war victims. Only the 1960-1970 have witnessed a virtue explosion of research in mental health through neurophysiology and neurochemistry scientific discoveries, which offer small but encouraging glimmerings of the correlation between psychological processes and the physical structures of the brain. According to Wilson, Herbert & Shiel (2003)[54] in designing an RCog program, the health professional must have knowledge about the functional anatomy of the brain (neuropsychology); cognitive models that explain certain behaviors (cognitive psychology) and flexible and adapted strategies for patients with cerebral dysfunction (behavioral psychology). In Portugal, there are Institutions that highlight the Rcog holistic approch, such as the "*Centro de Reabilitação Profissional de Gaia*" that in addition to the focus on patient recovery and family support, it also includes professional (re) integration in the recovery plan.

The RCog intervention implies the accomplishment of training sessions with variable frequency, duration and intensity (complexity) and of basic skills essential for complex daily cognitive domains good performance. An example is the attention training model that demonstrates an improvement in independent mnesic and executive tasks (not previously trained) that require the same skills.[55] It should take place preferably in clinical environments simultaneously structured according to the individual's real context.[56] It is therefore indicated, in some cases, that the direct support cognitive intervention can be developed at home or in community day centers.

One of the main RCog techniques to reduce memory changes in daily routine activities is the use of compensatory strategies with external aids. These strategies are based on the assumption that it is possible to compensate cognitive limitations through techniques that help in the processes of retention and memory recovery, such as establishing well-defined scheduled routines; tidying personal objects always using the same logic and ordering; reorganize the everyday family environment in a systematic way using alerts such as alarms, calendars and clocks. It is fundamental to realize that it is possible to train memory with organization rather than with repetition.

In memory training, techniques based on internal reorganiza-

tion strategies can also be applied, such as auditory-verbal and visual mnemonics. The use of visual imagery is widely recommended as it promotes the connection of elements that are typically remote and explores visuospatial relationships.[53] Internal verbal strategies focus on the establishment of facilitating semantic or phonological associations in elements called acronyms, which refer to the grouping of the initial letters of several words, forming an easily pronounced abbreviation (eg. WHO or AIDS). Or through the creation of a story that associates a lot of information in an integrated and logical way. This will later help the recall mechanism called *acrostics*, which are textual forms that combine the first letter of each sentence to form a word.[53]

In general, systematic learning without errors is the most effective way to consolidate new learning in situations where mistakes are allowed.[57,58] For example, in the early stages of Alzheimer's disease, when it is possible to intervene on memory problems, a method of learning without errors can be advantageous in these cases.[59]

In summary, regarding the holistic approach in RCog, it is important to highlight some guiding principles:

- it should not be isolated from other therapeutic approaches when indicated, whether pharmacological or nonpharmacological;
- cognitive training must be structured based on an increasing hierarchy of difficulty and complexity;
- the learning of visual imagery and mnemonic strategies should be promoted, using external aids and environmental modification.

eHealth technologies applied to cognitive diseases treatment

In a world of rapid technological growth, companies and researchers have developed increasingly efficient tools in telerehabilitation promoting improvements in access to healthcare and in the cost-benefit ratio, both for clinical providers and for users.

Tele-rehabilitation in neuropsychology can be defined as the provision of cognitive rehabilitation services through information and communication technologies (ICT), including assessment, monitoring, prevention, intervention, supervision, education and counseling by a group of qualified professionals.[60] This type of service is expanding access to mental health care for people in rural areas, who may live hundreds of miles from the nearest provider.[61] The intervention can be ensured by videoconferencing platforms such as Skype or Zoom or by specific equipment with emphasis on virtual reality[62]; neurofeedback; non-invasive brain stimulation and a set of software available in applications and sites. The evolution of neurofeedback is an example of significant technological advances in this area, since, in the 1960s, it was practically exclusively for use by the National Aeronautics and Space Administration.[63]

Regarding softwares and regarding Nussbaum and his team (2019)[64] its increasing success results from making it easy to monitor the patient's health status; being available in any context (e.g. home, work); offering stimulating and modifiable interface according to the user's characteristics and it is low cost. Another advantage is the possibility of adapting the parameters of complexity and specificity of tasks according to the patient's performance, this customized training results in additional motivation.[65]

In an extensive review of cognitive training applications for various pathologies in adults and in the elderly, 14 applications for stroke were described; seven for traumatic brain injury and 29 for cognitive intervention in general.[64] Recently in a review by Bogdanova, Yee, Ho & Cicerone (2015)[66] focused on 28 neurorehabilitation programs using ICT to train attention; memory and executive functions of patients with acquired brain injury, significant improvements were found in 23. In Portugal, Miguel e Luz (2012)[67] surveyed 12 applications in Portuguese that can be used anywhere.

Particularly noteworthy are Cogweb and Rehacom or a more recent version - Cogniplus - used in clinical, institutional and hospital settings by neuropsychologists or trained health professionals. The enormous development of these technologies has also been followed in our country by the team of researchers Faria and Badia (2015)[65] with the specific creation of the NeuroReahLab Task Gebnerator used with patients suffering from cerebrovascular disease, as it allows to easily generate neurostimulation tasks for domain training specific executives of higher nerve functions. RCog using ICT is thus a non-pharmacological therapeutic approach within the scope of applied neuropsychology based on the machine-person interaction with high preventive potentialities in mental health in the elderly. It can be combined with other quantifiable measures, such as psychophysiological and biosignals records developed by teams of researchers in biophysicists and biomedical engineering.[63]

Conclusion

In dead neuropsychologists and geropsychologists in Portugal seem nowadays to be broadening their reach via social platforms to diverse audience, sharing more mental health advice and clinical researchers are releasing results earlier which promotes more timely humanized health care. The American Psychological Association (2002) *Ethics Code*[68] and the deontological code of the Portuguese Order of Psychologists (2011)[69] encourages professionals to respect rights, dignity and well-being by eliminating the effect of cultural and sociodemographic stereotypes and prejudices, such as age. This prejudice strengthens the belief that age inevitably implies dementia; that older adults have high rates of mental illness

because they are more fragile or are more socially isolated. But, with high relevance, research has also shown that many older adults are resilient and in good health[70] managing to adapt to life transitions with personal and interpersonal development.[71]

For all these evidences described here, the human brain aging imposes a huge health and economic burden on modern society. It is a constant challenge for clinical practice in geriatric neuropsychology, the attribution of the various variables to underlying pathological conditions or to healthy changes in the senescent process itself.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram não possuir conflitos de interesse.

Suporte Financeiro: O presente trabalho não foi suportado por nenhum subsídio ou bolsa.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of interest: The authors have no conflicts of interest to declare.

Financial Support: This work has not received any contribution grant or scholarship.

Provenance and Peer Review: Not commissioned; externally peer reviewed.

ORCID iD: André Carvalho https://orcid.org/0000-0001-9507-5686

References

1. de Sousa Faria MC. Health Promotion and Wellness in Aging. In: Handbook of Research on Health Systems and Organizations for an Aging Society. London: IGI Global; 2020. p.12-28.
2. Schaie KW, Willis SL. Handbook of the psychology of aging. New York: Academic Press; 2010.
3. Craik FI, Salthouse TA. The handbook of aging and cognition. Chicago: Psychology press; 2011.
4. Park D, Schwarz N. Cognitive aging: A primer. Chicago: Psychology Press; 2012.
5. Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, Burke JR, Hurd MD, Potter GG, Rodgers WL, Steffens DC, Willis RJ, Wallace RB. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology. 2007;29:125-32. doi: 10.1159/000109998.
6. McCurry SM, Logsdon RG, Teri L, Vitiello MV. Evidence-based psychological treatments for insomnia in older adults. Psychol Aging. 2007;22:18-27. doi: 10.1037/0882-7974.22.1.18.
7. Günak M, Billings J, Carratu E, Marchant NL, Favarato G, Orgeta V. Post-traumatic stress disorder as a risk factor for dementia: systematic review and meta-analysis. Br J Psychiatry. 2020;217:600-8. doi: 10.1192/bjp.2020.150.
8. Blazer D, Le M, Maslow K, Eden J, editors. Committee on the Mental Health Workforce for Geriatric Populations; Board on Health Care Services. Chicago: Institute of Medicine;2012.
9. Lichtenthal WG, Cruess DG, Prigerson HG. A case for establishing complicated grief as a distinct mental disorder in DSM-V. Clin Psychol Rev. 2004;24:637-62. doi: 10.1016/j.cpr.2004.07.002.
10. Palmer BW, Folsom D, Bartels S, Jeste DV. Psychotic disorders in late life: Implications for treatment and future directions for clinical services. Generatin. J Am Soc Aging. 2002;26:39-43.
11. Carvalho A. Depressão e outras perturbações mentais comuns. Enquadramento global e nacional e referência de recurso em casos emergentes. Lisboa: Programa Nacional para a Saúde Mental; 2017.
12. Carvalho AD, Mateus P, Nogueira PJ, Farinha CS, Oliveira AL, Alves MI, Martins J. Portugal Saúde Mental em Números. Lisboa: Direção Geral da Saúde; 2016.
13. Gonçalves-Pereira M, Cardos A, Verdelho A, da Silva JA, de Almeida MC, Fernandes A, Xavier M. The prevalence of dementia in a Portuguese community sample: a 10/66 Dementia Research Group study. BMC Geriatr. 2017;17:261. doi: 10.1186/s12877-017-0647-5.
14. Santana I, Farinha F, Freitas S, Rodrigue V, Carvalho ÁEpidemiologia da Demência e da Doença de Alzheimer em Portugal: Estimativas da Prevalência e dos Encargos Financeiros com a Medicação. Acta Méd Port. 2015;28:182-8.
15. Nunes B, Silva RD, Cruz VT, Roriz JM, Pais J, Silva MC. Prevalence and pattern of cognitive impairment in rural and urban populations from Northern Portugal. BMC Neurol. 2010;10:42.
16. Garcia C, Costa C, Guerreiro M, Leitão O, Mendonça AD, Umbelino J. Estimativa da prevalência da demência e da doença de Alzheimer em Portugal. Acta Med Port. 1994;7:91.
17. Direção-Geral da Saúde. Abordagem terapêutica das alterações cognitivas. 2011: norma da DGS n. º 53/2011, de 27/12/2011. Lisboa: DGS; 20122.
18. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology.1994;34:939. doi: 10.1212/WNL.34.7.939.
19. Dubois B, Feldman HH, Jacova C, DeKosky ST, Barberger-Gateau P, Cummings J, et al.Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS–ADRDA criteria. The Lancet Neurology. 2007;6:734-46.
20. Román GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, et al. Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. Neurology. 1993;43:250. doi: 10.1212/WNL.43.2.250.
21. Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S A, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology. 1998;51:1546-54.
22. McKeith IG, Galask D, Kosaka K, Perry EK, Dickso DW, Hansen LA, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology. 1996;47:1113-24.
23. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, et al. Mild cognitive impairment–beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med. 2004;256:240-246. doi: 10.1111/j.1365-2796.2004.01380.x.
24. Chari D, Ali R, Gupta R. Reversible dementia in elderly: Really uncommon? J Geriatr Mental Health.2015;2:30. doi: 10.4103/2348-9995.161378.
25. Bäckman L, Jones S, Small BJ, Agüero-Torres H, Fratiglioni L. Rate of cognitive decline in preclinical Alzheimer's disease: the role of comorbidity. J Gerontol Series B: Psychol Sci Social Sci.2003;58:P228-P236.
26. National Research Council. The Aging Mind: Opportunities in Cognitive Research. Washington, DC: The National Academies Press; 2000. https://doi.org/10.17226/9783.
27. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol. 2011;10:819-28. doi: 10.1016/S1474-4422(11)70072-2.
28. Singh-Manoux A, Kivimaki M, Glymour MM, Elbaz A, Berr C, Ebmeier K P, et al. Timing of onset of cognitive decline: results from Whitehall II prospective cohort study. BMJ. 2012;344:d7622. doi: 10.1136/bmj.d7622.
29. Karlamangla AS, Lachman ME, Han W, Huang M, Greendale GA. Evidence for cognitive aging in midlife women: Study of women's health across the nation. PLoS One. 2017; 12:e0169008. doi: 10.1371/journal.pone.0169008.
30. Finger S, Eling P. Franz Joseph Gall: Naturalist of the mind, visionary of the brain. Oxford: Oxford University Press; 2019.

31. Damasio, H. Phineas Gage: The brain and the behavior. Rev Neurol. 2018;174:738-9.

32. Damasio AR. The somatic marker hypothesis and the possible functions of the prefrontal cortex. Philosophical Transac Royal Soc London. Series B: Biol Sci. 1996;351:1413-20. doi: 10.1098/rstb.1996.0125.

33. Llewellyn-Smith IJ, Verberne AJ. Central regulation of autonomic functions. Oxford: Oxford University Press; 2011.

34. Kreibig SD. Autonomic nervous system activity in emotion: A review. Biol Psychol.2010: 84:394-421. doi: 10.1016/j.biopsycho.2010.03.010.

35. Jänig W, Häbler HJ. Neurophysiological analysis of target-related sympathetic pathways–from animal to human: similarities and differences. Acta Physiol Scand. 2003;177:255-274.

36. Doidge N. The brain's way of healing: Stories of remarkable recoveries and discoveries. London: Penguin: 2015.ISBN-13:

37. Magalhães RJ. Modelação de padrões de conectividade cerebral funcional [Doctoral dissertation] 2013. [accessed Oct 2020] Available from: http://hdl.handle.net/1822/27775.

38. Pettigrew C, Soldan A. Defining cognitive reserve and implications for cognitive aging. Curr Neurol Neurosci Rep. 2019;19:1. doi: 10.1007/s11910-019-0917-z.

39. Basile G, Sardella A. From cognitive to motor impairment and from sarcopenia to cognitive impairment: a bidirectional pathway towards frailty and disability. Aging Clin Exp Res. 2020; 1-10. doi: 10.1007/s40520-020-01550-y.

40. Stern Y, Arenaza-Urquijo EM, Bartrés-Faz D, Belleville S, Cantilon M, Chetelat G. Reserve, Resilience and Protective Factors PIA Empirical Definitions and Conceptual Frameworks Workgroup. Whitepaper: defining and investigating cognitive reserve, brain reserve, and brain maintenance. Alzheimers Dement. 2020;16:1305-11. doi: 10.1016/j.jalz.2018.07.219.

41. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. The Lancet Neurology. 2012;11:1006-12. doi: 10.1016/S1474-4422(12)70191-6.

42. Meng X., D'arcy C. Education and dementia in the context of the cognitive reserve hypothesis: a systematic review with meta-analyses and qualitative analyses. PloS One. 2012;7:e38268. doi: 10.1371/journal.pone.0038268.

43. Xu W, Tan L, Wang HF, Tan MS, Tan L, Li J, et al. Education and risk of dementia: dose-response meta-analysis of prospective cohort studies. Mol Neurobiol.2016;53:3113-23. doi: 10.1007/s12035-015-9211-5.

44. Wang HX, Dekhtyar S, Fratiglioni L, Herlitz A. Childhood school performance, education, and occupational complexity: A life course study from the kungsholmen project. Alzheimer Dement. 2020;7:P200. doi:10.1093/ije/dyw008.

45. Scarmea N, Stern Y. Cognitive reserve and lifestyle. J Clin Exp Neuropsychol. 2003;25:625-33. doi: 10.1076/jcen.25.5.625.14576.

46. Kuiper JS, Zuidersma M, Voshaar RC, Zuidema SU, Van den Heuvel ER., Stolk RP, et al. Social relationships and risk of dementia: A systematic review and meta-analysis of longitudinal cohort studies. Ageing Res Rev. 2015;2:39-57. doi: 10.1016/j.arr.2015.04.006.

47. Penninkilampi R, Casey AN, Singh MF, Brodaty H. The association between social engagement, loneliness, and risk of dementia: a systematic review and meta-analysis. J Alzheime Dis. 2018;66:1619-33. doi: 10.3233/JAD-180439.

48. Gould E, Beylin A, Tanapat P, Reeves A, Shors TJ. Learning enhances adult neurogenesis in the hippocampal formation. Nature Neurosci. 1999;2:260-5. doi: 10.1038/6365.

49. Van Praag H, Kempermann G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nature Neurosci. 1999;2:266-70. doi: 10.1038/6368.

50. Eriksson PS, Perfilieva E, Björk-Eriksson T, Alborn AM, Nordborg C, Peterson DA, et al. Neurogenesis in the adult human hippocampus. Nature Med. 1998;4:1313-7. doi: 10.1038/3305.

51. Bottino CM, Carvalho IA, Alvarez AM, Avila R, Zukauskas PR, Bustamante SE, et al. Cognitive rehabilitation combined with drug treatment in Alzheimer's disease patients: a pilot study. Clin Rehabil. 2005;19: 861-9.

52. Pascual-Leone A, Amedi A, Fregni F, Merabet LB. The plastic human brain cortex. Annu Rev Neurosci. 2005;28:377-401. doi: 10.1146/annurev.neuro.27.070203.144216.

53. Nunes B. Memória: Funcionamento, perturbações e treino. Porto: Lidel. 2008.

54. Wilson BA, Herber M, Shiel A. Behavioural approaches in neuropsychological rehabilitation. Berlin: Taylor & Francis; 2003.

55. Sohlberg MM, Mateer CA. Training use of compensatory memory books: a three-stage behavioral approach. J Clin Exp Neuropsychol. 1989;11:871-891. doi: 10.1080/01688638908400941.

56. Maggio MG, De Luca R, Molonia F, Porcari B, Destro M, Casella C, et al. Cognitive rehabilitation in patients with traumatic brain injury: A narrative review on the emerging use of virtual reality. J Clin Neurosci. 2019;61:1-4.

57. Wilson BA, Baddeley A, Evans J, Shiel A. Errorless learning in the rehabilitation of memory impaired people. Neuropsychol Rehabil. 1994;4:307-26.

58. Squires EJ, Hunkin NM, Parkin AJ. Errorless learning of novel associations in amnesia. Neuropsychologia. 1997; 35: 1103-11. doi: 10.1016/S0028-3932(97)00039-0.

59. Clark RC, Nguyen F, Sweller J. Efficiency in learning: Evidence-based guidelines to manage cognitive load. London: John Wiley & Sons; 2011.

60. Brennan D, Tindal L, Theodoros D, Brown J, Campbell M, Christiana D, et al. A blueprint for telerehabilitation guidelines. Int J Telerehabil. 2010;2:31. doi: 10.5195/ijt.2010.6063.

61. Bagchi AD, Melamed B, Yeniyurt S, Holzemer W, Reyes D. Telemedicine delivery for urban seniors with low computer literacy: A pilot study. Online J Nurs Informatics. 2018; 22.

62. Chen B, Moreland J, Zhang J. Human brain functional MRI and DTI visualization with virtual reality. In World Conference on Innovative Virtual Reality; 2011343-9. doi: 10.1115/WINVR2011-5565.

63. Leal I. Intervenção em Ciberpsicologia. Lisboa: Pactor; 2019.

64. Nussbaum R, Kelly C, Quinby E, Mac A, Parmanto B, Dicianno BE. Systematic review of mobile health applications in rehabilitation. Arch Phys Med Rehabil. 2019;100:115-27. doi: 10.1016/j.apmr.2018.07.439.

65. Faria AL, Badia SB. Development and evaluation of a web-based cognitive task generator for personalized cognitive training. Proceedings of the 3rd 2015 Workshop on ICTs for improving Patients Rehabilitation Research Techniques. REAHB. 2015;1-4. doi: 10.1145/2838944.2838945.

66. Bogdanova Y, Yee MK, Ho VT, Cicerone KD. Computerized Cognitive Rehabilitation of Attention and Executive Function in Acquired Brain Injury: A Systematic Review. J Head Trauma Rehabil. 2016;31:419-33. doi: 10.1097/HTR.0000000000000203.

67. Miguel I, da Luz HA. New techonologies towards cognitive stimulation in elderly with dementia: Effects and potential. In: 2015 10th Iberian Conference on Information Systems and Technologies (CISTI) IEEE. doi: 10.1109/CISTI.2015.7170369.

68. American Psychological Association. Criteria for practice guideline development and evaluation. Am Psychol. 2002;57:1048-51.

69. Ordem dos Psicólogos Portugueses. Código deontológico da ordem dos psicólogos Portugueses. Diário da República, 2ª série, 17931, 17936; 2011.

70. Depp CA, Jeste DV. Definitions and predictors of successful aging: a comprehensive review of larger quantitative studies. Am J Geriatr Psychiatry. 2006;14:6-20. doi: 10.1097/01.JGP.0000192501.03069.bc.

71. Hill R. Positive aging. New York: WW Norton; 2005.