

COGNITIVE RESERVE AS A PREDICTOR OF HEALTHY AGING

Eduardo Valenciano-Mendoza Joan Guàrdia-Olmos

Facultat de Psicologia. Universitat de Barcelona. GISME-UB

Abstract: Many studies point out the existence of individual differences both in the levels of age-related cognitive impairment and in the way this impairment occurs: some people can tolerate brain damage for a longer time without showing external signs of damage. The concept of cognitive reserve emerges as a useful and interesting approach to explain this phenomenon. This paper attempts to describe the state of the question as regards the cognitive reserve. It refers to an active process by which the brain adapts itself to a situation of impairment by using cognitive resources in order to compensate this impairment. It is a concept that cannot be measured directly but through indirect indicators. The most common indicators to measure the cognitive reserve are: level of education, occupation attainment and lifestyle. Many studies suggest that high values in these indicators go together with a high level of cognitive reserve and, therefore, play an important protective function against the development of dementia. We conclude this article with a set of practical recommendations to stimulate the cognitive reserve and age healthy.

Keywords: cognitive reserve, brain reserve, aging, mild cognitive impairment, dementia, cognitive damage, active and healthy ageing.

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Introduction

Aging is usually associated with cognitive impairment and an increasing risk of suffering dementia (Giogkaraki, Michaelides & Constantinidou, 2013). Estimates at a global scale point out that around 7% of the population over 65 suffer dementia. In developed countries this percentage can increase up to 10% (Méndez & Cummings, 2003). The sharp increase in life expectancy that has occurred throughout the last

century in the vast majority of developed countries has brought about a drawback: a rise in the number of people who suffer one form of dementia or another.

There are different degrees and types of dementia, from mild alterations with a low impact on the quality of life to levels of cognitive impairment that cause a notorious effect in people's capacity to live independently (Kandel, Schwartz, Jessel, Siegelbaum, Hudspeth, 2013).

However, there are important differences both on the levels of cognitive impairment and in the way this impairment occurs. In addition, there is no linear relationship between the degree of brain pathology and the clinical expression. In other words, some individuals tolerate brain damage for a longer time without showing external signs of impairment.

Consequently, it seems appropriate to ask for the cause of these interindividual differences and, for that reason, the concept of cognitive reserve emerges as a useful and interesting approach to this phenomenon (Giogkaraki et al., 2013).

The concept of cognitive reserve (versus brain reserve)

First of all, it is important to make a distinction between two concepts that are usually confused: brain reserve and cognitive reserve. The concept of brain reserve refers to the differences in brain size and its constituents (for instance, neurons and synapses) that explain differences in the patients' susceptibility towards brain pathology (Barulli & Stern, 2013). Therefore, brain reserve is a quantitative notion, that is, it can be measured directly (the bigger the brain size, the greater the number of neurons and, therefore, the greater the brain reserve).

However, the concept of cognitive reserve involves an active process by which the brain adapts itself to a situation of impairment by using cognitive resources in order to compensate this impairment (Stern, 2007). In that sense, the cognitive reserve can be understood as a capacity that makes it possible to postpone the appearance of clinic signs of dementia once the pathology has already started (Singh-Manoux et al. 2011; Premi et al., 2013). All in all, through the cognitive reserve we evaluate brain function, whereas when we talk about brain reserve we focus on the brain size (Stern, 2012).

The cognitive reserve involves an active process by which the same brain damage or pathology produces different effects depending on the person, even if the

brain size stays constant (Stern, 2012). In contrast with the brain reserve, the cognitive reserve is a concept that cannot be observed and, therefore, it cannot be measured directly. For that reason, Jones et al. (2011) recommend using models which make it possible to statistically analyze the relationship between different indicators associated with the cognitive reserve with the presence or absence of cognitive impairment in adults.

A great number of investigations suggest that age-related cognitive impairment is selective given that it affects different brain areas to different degrees. Specifically, the cortical areas from the prefrontal, inferior temporal lobe as well as the hippocampus are the most affected due to the process of age-related cognitive impairment. At the same time, aging goes together with a lower reuptake efficiency of the neurotransmitters as well as a decrease in the speed of the synaptic signal transmission (Wu, Oh & Distenhof, 2002; cited by Giogkaraki et al. 2013).

Based on the above considerations, it seems logical to think that aging produces, among other alterations, impairment in the superior cognitive functions such as memory, learning, concept formation, categorization, and cognitive flexibility or functions related to calculus.

Relationship between cognitive reserve and healthy aging

The vast majority of studies aiming to prove the role that the cognitive reserve plays in terms of prevention of cognitive impairment follow the same logic. That is, defining the cognitive reserve as the variable to be explained and analyzing its statistical relationship with several indicators of cognitive impairment. There is a plurality of tests that measure cognitive capacities and that are used as performance indicators. It has been empirically proved that performance diminishes as people get older (Giogkaraki et., 2013). Therefore, many of the current investigations analyze whether impairment is due to age and whether we can consider it normal or else it is a symptom of a more serious pathology and a prelude of dementia.

Those variables used to determine the level of cognitive reserve tend to be indirect indicators of the cognitive reserve, and those more frequently used are variables related to life experiences (Stern, 2009) such as the level of studies, the professional status, the intellectual level and the participation in leisure, cultural, social and cognitive activities. These experiences can influence brain anatomy, increasing

cell production and blood vessels in such a way that they promote neural plasticity and improve the reserve. Following this idea, an increase in the frequency of our everyday activities that involve the use of cognitive resources can prevent a pathology associated with cognitive impairment (Scarmeas & Stern, 2003).

In a study carried out by Stern et al. (1994) they found that individuals with less than eight years of education had 2.2 times higher risk of developing dementia as compared to those individuals with more years of education. In the same study, they proved that subjects with a lower occupational attainment had 2.25 times higher risk of developing dementia as compared to subjects with a higher occupational attainment. These results seem to suggest that the higher the education and the occupation attainment, the more cognitive reserve to cope with age-related dementia. In a study published some years later, Scarmeas et al. (2001; cited by Stern, 2012) aimed to evaluate the influence of participation in leisure activities – such as hiking, going to a movie, reading magazines or books and even watching television – when it comes to the likelihood of developing dementia. The investigators concluded their study by stating that those individuals who, on a regular basis, participated in leisure activities like the ones mentioned above had 38% lower risk of developing dementia. These studies point out that vital experiences such as the years of education, the occupational attainment and the participation in leisure activities have a protective effect in terms of developing dementia (Stern, 2012). In other words, these vital experiences build up a greater cognitive reserve that protects us from dementia up to a certain point.

However, we can observe a phenomenon that, at first sight, could seem contradictory. Despite the fact that these experiences diminish the probability of developing dementia, it is also true that those individuals with a higher index of cognitive reserve who suffer dementia experience a quicker cognitive decline. The following figure (number 1) illustrates this process very clearly.

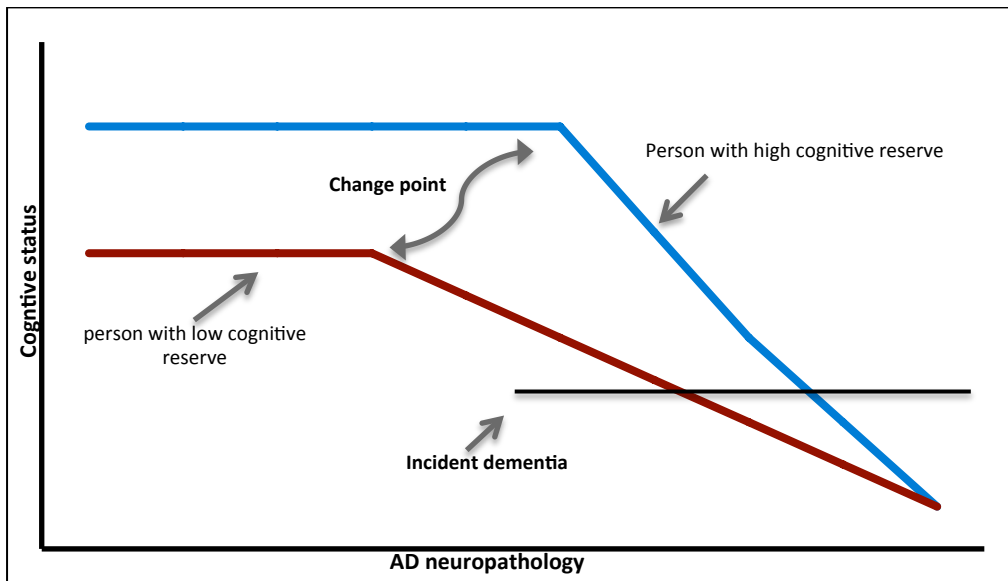


Figure 1. Evolution of cognitive functions in relation to the neuropathology related to Alzheimer's disease. Re-elaborated based on: Barulli & Stern (2013).

Figure 1 illustrates two cases: one subject with a high cognitive reserve and another subject with a considerably smaller cognitive reserve. In the vertical axis are represented the subject's cognitive capacities and, in the horizontal axis, brain damage as a consequence of suffering Alzheimer's disease. As we mentioned previously, subjects who show a greater cognitive reserve are individuals with more education, a better occupation and who carry out cognitively-stimulating leisure activities. For that reason, individuals with a high cognitive reserve show greater cognitive capacities. In other words, subjects with a high cognitive reserve perform better in tests measuring cognitive capacities in comparison with subjects with a lower cognitive reserve.

Likewise, subjects with a higher cognitive reserve – therefore with greater cognitive capacities – show clinical signs of dementia later in life, as compared to subjects with a lower cognitive reserve – therefore with lower cognitive capacities. However, once subjects with a high cognitive reserve show clinical signs of dementia, cognitive impairment occurs much more quickly than in subjects with a low cognitive reserve. This phenomenon – apparently contradictory – should not lead us to think that the cognitive reserve does not play a protective role against dementia. What actually happens is that individuals who suffer from dementia but have a high cognitive reserve are able to cope with this dementia for a longer time without showing clinical signs of it, that is to say, without having their performance affected. On the contrary, subjects with a lower cognitive reserve start to show clinical signs of dementia much earlier.

One of the disorders that older people present more frequently is the one called Mild Cognitive Impairment (MCI), which involves a diagnostic entity that appears and is diagnosed according to the following criteria (Peterson, 2004; Albert et al., 2011):

- Presence of changes in the cognitive function, preferably corroborated by close informants, namely relatives. The subject shows changes in his everyday life functioning and his daily activities.
- Lower performance than expected taking into account his age and educational attainment in one or several cognitive domains, that is, in the different cognitive tasks that human beings conduct. For example, in tasks implying memory, language, mathematical thinking, etc.
- Functional capacities preserved or minimally affected: this implies that despite these mild cognitive errors, the subject is capable of conducting his daily activities with a great degree of normality.
- Dismissing the existence of dementia in an early stage.

We can distinguish two main subtypes of MCI, amnesic and non-amnesic, taking into account whether episodic memory is affected or not (Albert et al., 2011). Episodic memory is a type of memory characterized by the fact that people are able to remember past events from their lives with normality and, therefore, they have an effective memory of the important events of their lives. Apart from impairment in episodic memory, impairment related to working memory has also been detected in individuals with MCI, which is related to processing resources involved in the vast majority of everyday life activities (Gagnon & Belleville, 2011). Working memory is another type of memory which is characterized by being a resource we use when we carry out a task that requires us to keep something in our memory for a short period of time, for example, when we retain a phone number before dialing it.

In a review carried out by Lojo, Facal and Juncos (2012), it was observed that the cognitive reserve influences the delay in the appearance of the symptoms of MCI. Individuals with higher levels of education (Mejía, Gutiérrez, Villa, and Ostrosky-Solis, 2004; Kawano et al., 2010; Radanovic et al., 2009) and who frequently participate in leisure activities (Verghese et al., 2006) and cognitive activities (Wilson, Scherr, Schneider, Tang, & Bennett, 2007) show better

cognitive performance and a lower risk of impairment. In addition, it has been observed that people with greater intelligence show a greater neuropathological process, as compared to people of less intelligence who show a similar cognitive performance (Solé-Padullés et al., 2009; Bosch et al., 2010). This fact makes evident the compensatory effect occurring in individuals with a high cognitive reserve: it masks neuropathological impairment through a milder manifestation of clinical symptoms than would be expected of subjects with the same neuropathological impairment and a lower cognitive reserve.

Evidence from epidemiologic studies point out that life experiences – even those taking place later in life – can positively influence the increase of the cognitive reserve (Stern, 2012). These results are of great importance given that they show that it is possible to intervene in the cognitive reserve during aging and, therefore, to reduce the age-related cognitive decline. Other studies (Kramer et al., 1999) show, for instance, the benefits of aerobic exercise in the sense that it leads to better cognitive performance.

Based on the above considerations, it seems that the concept of cognitive reserve is closely linked to the manifestation of cognitive impairment, especially during old age. Hence, we should consider that having a high cognitive reserve can become a mechanism of prevention of impairment and, therefore, it is associated with healthy aging in those individual with resources at their disposal. A simple scheme to understand the elements that compose the cognitive reserve is the following figure:

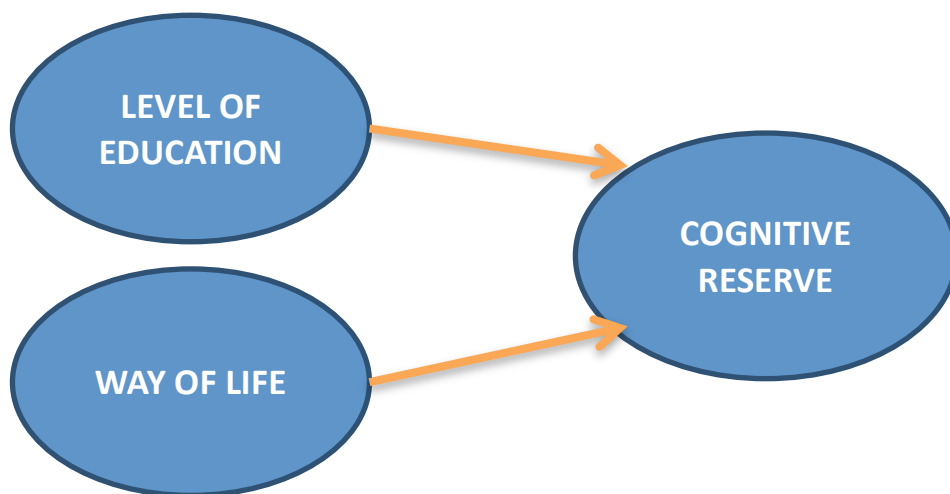


Figure 2. Cognitive reserve model and its indicators

Obviously, it is still necessary to establish how every single concept is filled in. Regarding the level of education, it seems clear, given that we have an evident indicator such as the subject's years of education, by adding the following:

- Years of education (already mentioned)
- Complexity of the tasks carried out at work. The greater the complexity, the higher the cognitive reserve
- Reading habits in terms of frequency.
- Crystallized Intelligence, that is, the part of intelligence that is acquired in interaction with the sociocultural atmosphere. Hence, it is a kind of intelligence that can be developed, especially through the acquisition of new learning, and it is closely related to experience.

The second element is much more complicated. In fact, in order to determine if the lifestyle promotes the cognitive reserve, we need to pay attention to the following indicators:

- Social activities, in the sense that they increase the levels of the cognitive reserve if the person has a good social activity: being a member of associations, being involved in them, common projects, sports activities and similar ones are a few good examples.
- Cultural activities: following the same idea as in the previous point but in the cultural domain. Therefore, going to a play, a movie, conferences and other related activities are good examples of cultural stimulation.

Recommendations

The universalization of education in the vast majority of developed countries as well as its compulsory nature up to a certain educational level are crucial achievements which have led to enormous social breakthroughs. In fact, as has been mentioned throughout this paper, among other benefits, compulsory education and its universalization are closely linked to a greater cognitive reserve, the latter being a key tool to resist cognitive decline and age-related dementia. However, the number of years of education is only one among the many factors involved in the development of a cognitive reserve. Below we introduce a set of recommendations based on results from

a wide range of studies on this topic (Lojo et al., 2012; Vasile et al., 2013). The reader will see that it is never too late to put them into practice. Despite the fact that research on the factors behind the cognitive reserve is not conclusive, the recommendations that follow are harmless and, according to a wide range of studies, they seem to have a special influence on the cognitive reserve as long as they are put into practice frequently.

- 1) Cognitively-stimulating activities (studying, reading, watching films, listening to music...)
- 2) Job with a certain degree of complexity (requiring the constant use of strategies to solve problems)
- 3) Regular physical exercise (walking, aerobic exercise)
- 4) Social activities (participation in associations, voluntary work)
- 5) Active and healthy lifestyle.

References

- Albert, M.S., DeKosky, S.T, Dickson, D., Dubois, B., Feldman, H.H., Fox, N.C. ... Phelps, C.H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, 7, 270–279.
- Albert, S.M. & Teresi, J.A. (1999). Reading ability, education, and cognitive status assessment among older adults in Harlem. *American Journal of Public Health*, 89(1), 95–97. doi:10.2105/AJPH.89.1.95
- American Psychiatric Association (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev. ed.). Washington, DC: American Psychiatric Association.
- Barulli, D. & Stern, Y. (2013). Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. *Trends in Cognitive Sciences*, 17 (10), 502-509. doi:10.1016/j.tics.2013.08.012
- Benedet, M. J., & Alejandre, M. A. (1998). *TAVEC: Test de aprendizaje verbal España- complutense*. Madrid: TEA Ediciones.

- Benedet, M. J., & Seisdedos, N. (1996). *Evaluación clínica de las quejas de la memoria en la vida cotidiana*. Madrid: Editorial Médica Panamericana.
- Bosch, B., Bartrés-Faz, D., Rami, L., Arenaza-Urquijo, E. M., Fernández-Espejo, D., Junqué, C. ...Molinuevo, J.L (2010). Cognitive reserve modulates task-induced activations and deactivations in healthy elders, amnesic mild cognitive impairment and mild alzheimer's disease. *Cortex: A Journal Devoted to the Study of the Nervous System and Behavior*, 46(4), 451-461.
doi:10.1016/j.cortex.2009.05.006
- Case, R., Kurland, M. D., & Goldberg, J. (1982). Operational efficiency and the growth of short-term memory span. *Journal of Experimental Child Psychology*, 33(3), 386-404. doi:10.1016/0022-0965(82)90054-6
- Daneman, M., & Carpenter, P. A. (1980). Individual differences in working memory and reading. *Journal of Verbal Learning and Verbal Behavior*, 19(4), 450-466. doi:10.1016/S0022-5371(80)90312-6
- Dubois, B., & Albert, M. L. (2004). Amnesic MCI or prodromal Alzheimer disease. *Lancet*, 3(4), 246-258. doi:10.1016/S1474-4422(04)00710-0
- Dubois, B., Feldman, H. H., Jacova, C., Dekosky, S. T., Barberger- Gateau, P., Cummings, J. ...Scheltens, P. (2007). Research criteria for the diagnosis of Alzheimer's disease: Revising the NINCDS-ADRDA criteria. *Lancet Neurology*, 6(8), 734-746. doi:10.1016/S1474-4422(07)70178-3
- Folstein, M. F., Folstein, S. E., & McHogh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12, 189-198.
- Gagnon, L. G., & Belleville, S. (2011). Working memory in mild cognitive impairment and Alzheimer's disease: Contribution of forgetting and predictive value of complex span tasks. *Neuropsychology*, 25(2), 226-236.
doi:10.1037/a0020919
- Garibotto, V., Borroni, B., Kalbe, E., Herholz, K., Salmon, E., Holtoff, V. ...Perani, D. (2008). Education and occupation as proxies for reserve in aMCI converters and AD FDG-PET evidence. *Neurology*, 71(17), 1342-1349.
doi:10.1212/01.wnl.0000327670.62378.c0
- Gauthier, S., Resiveberg, B., Zaudig, M., Petersen, R. C., Ritchie, K., Broich, K. ... Winblad, B. (2006). Mild cognitive impairment. *Lancet*, 367(9518), 1262-1270. doi:10.1016/S0140-6736(06)68542-5

- Giogkaraki, E., Michaelides, M. P., Constantinidou, F. (2013). The role of cognitive reserve in cognitive ageing: results from the neurocognitive study on aging. *Journal of Clinical and Experimental Neuropsychology*, 35 (10), 1024-1035. doi: 10.1080/13803395.2013.847906
- Greenaway, M.C., Lacritz, L.H., Binegar, Weiner, M.F., Lipton, A., Munro, C. (2006). Patterns of verbal memory performance in mild cognitive impairment, Alzheimer disease, and normal aging. *Cognitive and Behavioral Neurology*, 19, 79-84.
- Jones, R. H., Manly, J., Glymour, M. M., Rentz, D. M., Jefferson, A. L., & Stern, Y. (2011). Conceptual and measurement challenges in research on cognitive reserve. *Journal of the International Neuropsychological Society*, 17(4), 1-9. doi:10.1017/S1355617710001748
- Kandel, E. R., Schwartz, J. H.; Jessell, T. M., Siegelbaum, S. A., Hudspeth, A.J. (2012). *Principles of Neural Science*. New York: McGraw-Hill.
- Kawano, N., Umegaki, H., Suzuki, Y., Yamamoto, S., Mogi, N., & Iguchi, A. (2010). Effects of educational background on verbal fluency task performance in older adults with Alzheimer's disease and mild cognitive impairment. *International Psychogeriatrics. Special Issue: Focus on Training in Psychogeriatrics*, 22(6), 995-1002. doi:10.1017/S1041610210000839
- Kramer A.F., Hahn S, Cohen N.J., Banich M.T., McAuley E., Harrison C.R., Chason J., Vakil E., Bardell L., Boileau R.A., Colcombe A. (1999) Ageing, fitness and neurocognitive function. *Nature*, 400, 418–419.
- Lojo-Seoane, C., Facal, D., Juncos-Rabadán, O. (2012) ¿Previene la actividad intelectual el deterioro cognitivo? Relaciones entre reserva cognitiva y deterioro cognitivo ligero. *Revista Española de Geriatría y Gerontología*. Avance publicación online. doi:10.1016/j.regg.2012.02.006
- Mejía, S., Gutiérrez, L. M., Villa, A. R., & Ostrosky-Solís, F. (2004). Cognition, functional status, education, and the diagnosis of dementia and mild cognitive impairment in Spanish-speaking elderly. *Applied Neuropsychology*, 11(4), 194-201. doi:10.1207/s15324826an1104_4
- Mendez, M. F. & Cummings, J. L. (2003). *Dementia: a clinical approach*. Philadelphia: Butterworth-Heinemann
- Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine*, 256(3), 183-194. doi:10.1111/j.1365-2796.2004.01388.x

- Premi, E., Garibotto, V., Gazzina, S., Grassi, M., Cosseddu, M., Paghera, B., Turla, M., Padovani, A. & Borroni, B. (2013). Beyond cognitive reserve: behavioural reserve hypothesis in frontotemporal dementia. *Behavioural Brain Research*, 245, 58-62. doi: 10.1016/j.bbr.2013.01.030
- Radanovic, M., Diniz, B. S., Mirandez, R. M., da Silva Novaretti, T. M., Kneese Flacks, M., Yassuda, M. S., & Forlenza, O.V. (2009). Verbal fluency in the detection of mild cognitive impairment and Alzheimer's disease among Brazilian Portuguese speakers: The influence of education. *International Psychogeriatrics*, 21(6), 1081-1087. doi:10.1017/S1041610209990639
- Ribeiro, F., Guerreiro, M., de Mendonça, A. (2007). Verbal learning and memory deficits in Mild Cognitive Impairment. *Journal of Clinical and Experimental Neuropsychology*, 29, 187-197.
- Rodríguez N, Juncos- Rabadán O, Facal-Mayo D (2008). Discriminación mediante marcadores cognitivos del deterioro cognitivo leve frente al envejecimiento normal. *Rev Esp Geriatr Gerontol*, 43, 291-8.
- Rolstad, S., Nordlund, A., Eckerström, C., Gustavsson, M. H., Blennow, K., Olesen, P. J., ... Wallin, A. (2010). High education may offer protection against tauopathy in patients with mild cognitive impairment. *Journal of Alzheimer's Disease*, 21(1), 221-228.
- Roth, M., Tym, E., Mountjoy, C. Q., Huppert, F. A., Hendrie, H., Verma, S., & Goddard, R. (1986). CAMDEX. A standardised instrument for the diagnosis of mental disorders in the elderly with special reference to the early detection of dementia. *British Journal of Psychiatry*, 149, 698-709. doi:10.1192/bjp.149.6.698
- Scarmeas, N., & Stern, Y. (2003). Cognitive reserve and lifestyle. *Neuropsychology, Development, and Cognition. Section A, Journal of Clinical and Experimental Neuropsychology*, 25(5), 625-633. doi:10.1076/jcen.25.5.625.14576.
- Singh-Manoux, A., Marmot, M. G., Glymour, M., Sabia, S., Kivimäki, M. & Dugravot, A. (2011). Does cognitive reserve shape cognitive decline? *Annals of Neurology*, 70, 296-304. doi: 10.1002/ana.22391
- Solé-Padullés, C., Bartrés-Faz, D., Junqué, C., Vendrell, P., Rami, L., Clemente, I. C., ...Molinuevo, J. L. (2009). Brain structure and function related to cognitive reserve variables in normal aging, mild cognitive impairment and Alzheimer's

- disease. *Neurobiology of Aging*, 30(7), 1114-1124.
doi:10.1016/j.neurobiolaging.2007.10.008
- Soto-Añari, M., Flores-Valdivia, G., & Fernández-Guinea, S. (2013). Nivel de lectura como medida de reserva cognitiva en adultos mayores. *Revista de Neurología*, 56(2), 79- 85.
- Stern, Y., Gurland, B., Tatemichi, T.K., Tang, M. X., Wilder, D., Mayeux R. (1994). Influence of education and occupation on the incidence of Alzheimer disease. *JAMA*, 271, 1004-1010.
- Stern, Y. (2007). *Cognitive reserve. Theory and applications*. New York: Taylor & Francis.
- Stern, Y. (2009). Cognitive reserve. *Neuropsychologia*, 47(10), 2015-2028.
doi:10.1016/j.neuropsychologia.2009.03.004
- Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol*, 11 (11), 1006-1012. doi: 10.1016/S1474-4422(12)70191-6
- Sumowski, J. F., Wylie, G. R., DeLuca, J., & Chiaravalloti, N. (2010). Intellectual enrichment is linked to cerebral efficiency in multiple sclerosis: Functional magnetic resonance imaging evidence for cognitive reserve. *Brain: A Journal of Neurology*, 133(2), 362-374. doi:10.1093/brain/awp307
- Vasile, C. (2013). Cognitive reserve and cortical plasticity. *Procedia – Social and Behavioral Sciences*, 78, 601-604.
- Verghese, J., LeValley, A., Derby, C., Kuslansky, G., Katz, M., Hall, C., ...Lipton, R.B. (2006). Leisure activities and the risk of amnesic mild cognitive impairment in the elderly. *Neurology*, 66(6), 821-827.
doi:10.1212/01.wnl.0000202520.68987.48
- Wilson, R. S., Aggarwal, N. T., Barnes, L. L., Mendes de Leon, C. F., Hebert, L. E., & Evans, D. A. (2010). Cognitive decline in incident Alzheimer disease in a community population. *Neurology*, 74(12), 951-955.
doi:10.1212/WNL.0b013e3181d64786
- Wilson, R. S., Li, Y., Aggarwal, N. T., Barnes, L. L., McCann, J. J., Gilley, D. W., & Evans, D.A. (2004). Education and the course of cognitive decline in Alzheimer disease. *Neurology*, 63(7), 1198-1202.
doi:10.1212/01.WNL.0000140488.65299.53

Wilson, R. S., Scherr, P. A., Schneider, J. A., Tang, Y., & Bennett, D. A. (2007).
Relation of cognitive activity to risk of developing Alzheimer disease.
Neurology, 69(20), 1911-1920. doi:10.1212/01.wnl.0000271087.67782.cb