Chapter

The Role of Cognitive Reserve in Executive Functioning and Its Relationship to Cognitive Decline and Dementia

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Abstract

In this chapter, we explore how cognitive reserve is implicated in coping with the negative consequences of brain pathology and age-related cognitive decline. Individual differences in cognitive performance are based on different brain mechanisms (neural reserve and neural compensation), and reflect, among others, the effect of education, occupational attainment, leisure activities, and social involvement. These cognitive reserve proxies have been extensively associated with efficient executive functioning. We discuss and focus particularly on the compensation mechanisms related to the frontal lobe and its protective role, in maintaining cognitive performance in old age or even mitigating the clinical expression of dementia.

Keywords: cognitive reserve, executive functions, aging, cognitive decline, dementia

1. Introduction

The impact of brain aging on cognition is far from uniform, ranging from perfect fitness to cognitive impairment. The prevalence of dementia is estimated to increase from 57.4 million in 2019 to 152.8 million in 2050 [1], thus representing a major public health problem. Still, evidence shows that more than one-third of all cases of dementia could be prevented or modified by changes in lifestyle, correction of risk factors, and specific therapeutic interventions [2–5]. In fact, despite the absence of pharmacological treatment for degenerative diseases, such as Alzheimer's disease (AD), it is known that vascular risk factors increase the likelihood of cognitive decline. Simple measures, the control of hypertension, for instance, may revert cognitive impairment and reduce conversion to dementia [6]. Likewise, healthy lifestyle patterns, physical exercise, and intellectual and social enrichment may improve performance and change the biomarker trajectories of individuals classified as cognitively impaired [7–9].

Promoting the presence of protective factors throughout life may help to cope with the negative consequences of pathology through resilience or resistance mechanisms. The term "resistance" refers to the notion of avoiding pathology (i.e., being free from significant AD pathology) in the sense that it is inferred from an observed absence or lower level of dementia-associated brain injury, relative to an expected greater frequency or severity based on age, genetic factors, or other individual characteristics. On the other hand, "resilience" is mostly used in the sense of coping with pathology (i.e., remaining cognitively intact despite significant AD pathology) and is inferred from the observation of a higher than expected cognitive functioning related to the level of brain injury [10, 11]. While the first is linked to an absence or delay of brain changes ("brain maintenance"), the latter is closely associated with the concept of the reserve, which can be measured or inferred either as brain structural and/or physiological premorbid capacity [11, 12].

The construct of reserve firstly emerged to describe patients with extensive destruction of nervous tissue following brain damage but not the expected level of functional changes [13]. It was then proposed that larger brains, with greater weight and a larger number of neurons, could have protective effects on the cognitive decline due to a higher "brain reserve" capacity [14]. Years later, Stern [15] defined the concept of Cognitive Reserve (CR) as the brain's ability to optimize and maximize performance through the differential recruitment of brain networks or the use of alternative cognitive strategies to cope with brain dysfunction. Stern's proposal claims that the mechanisms underlying CR are active processes by which the brain tries to compensate for the neural loss. These processes can be influenced by the interaction between innate factors (e.g., in utero or genetically determined) and, mainly, lifelong experience (e.g., intelligence, education, occupation, physical exercise, leisure activities, or social involvement). In contrast, the passive models propose that response to neural damage is related to brain size or the number of synapses (brain reserve), which can affect the threshold for clinical expression [16]. Brain reserve and CR are not mutually exclusive in the sense that brain reserve does not protect against the accumulation of pathology, but it does protect against its negative effects [17]. Instead, they influence each other—life experiences and the involvement in stimulating cognitive activities can modify brain anatomy (i.e., neurogenesis, angiogenesis, and resistance to apoptosis) and positively regulate compounds that promote neural plasticity [18].

The concept of CR has progressively evolved in such a way that it is now central in the literature on normal and pathological aging, notwithstanding the theoretical pitfalls and methodological controversies generated by years of studies and reserve-associated concepts. The most striking challenges are the absence of an operational definition of CR and the lack of clarification of its neural bases, the relationship between the brain and CR, and which factors affect brain reserve [19]. Making an effort to overcome these difficulties, a consensus report tried to clarify CR terminology [17] by claiming "resilience" as an umbrella concept that describes the process of coping with age- and disease-related changes, which includes multiple reserve related-concepts, such as brain reserve, brain maintenance, and CR.

Normal aging is characterized by several brain changes at the morphometric and functional level, and associated neuropsychological changes, that are particularly relevant in the frontal lobes on which Executive Functions (EF) heavily depend upon [20]. Among other areas of cognition, EF play a critical role in everyday life, allowing individuals to plan ahead, focus attention, and switch between tasks, hence maintaining effective levels of independent functioning. Variable EF trajectories include

development into early adulthood and decline into older age, associated with structural and functional changes in the prefrontal cortex [21]. Despite this age-related decline, EF also assumes an important role in maintaining global cognitive efficiency in the late period of life, thanks to a higher CR [22].

There is considerable interest in understanding the processes underlying cognitive decline (and whether they result from specific or general impairments that reflect different patterns and different pathological processes) but also in how the brain actively copes with these deleterious effects on EF so functional independence can be maintained. Next in this chapter, we will review evidence that focuses on certain socio-behavioral CR proxies (e.g., education, occupational complexity, leisure activities, and social involvement), how they may help to cope with age-related changes and brain pathology, and how they relate with EF. Further, differences between "active" versus "passive" models of reserve and the underlying CR mechanism ("neural reserve" vs. "neural compensation") are described.

2. Socio-behavioral proxies in the prevention of cognitive decline and dementia

One of the major limitations of the CR construct is that it can hardly be measured directly. Three methods are usually used to quantify and measure it—(a) socio-behavioral indicators, (b) residual approach, and (c) functional neuroimaging studies [17]. Hence, studies should include not only measures of the status of the brain (reflecting brain alteration or pathology), but also clinical or cognitive performance (consequences of brain damage), and socio-behavioral indicators (e.g., an index of life-long experience/premorbid capacity) when assessing the role of CR. The goal is to be able to predict an individual's cognitive performance through the interaction between the proposed CR factors and the state of the brain/pathology.

Several studies have shown that CR proxies may decrease the rate of conversion to dementia in subjects with identical degrees of the pathological burden of AD [23, 24], and even have a protective role against the cognitive impairment associated with brain white-matter changes (WMC) or higher ventricular volume [25, 26] delaying the onset of clinical deficits [27]. Understanding the role of these proxies on the prediction of cognitive trajectories serves a two-fold objective, either it is disease prevention or disease diagnosis.

Different CR proxies have been identified [28], but recent systematic reviews indicate that education, occupational attainment, leisure activities, and social involvement are the most common indicators [29–31].

The number of years of formal education is the most consistently used across studies. A protective effect of education for age-associated cognitive decline appears to result in higher levels of CR [30, 32]. This is supported by strong positive associations between the number of years of formal education and crystallized measures (e.g., vocabulary) and EF, explaining, in the latter case, even more variance than age itself [33–35], compared with fluid abilities, such as processing speed, memory, or visuospatial abilities [34, 36, 37]. Robust scientific evidence also supports that lower-educated individuals are more likely to suffer from dementia in a wide range of settings [38]. For example, Contador et al. [39] found that living in a rural area (early and mid-life stages) increased the likelihood of dementia, with the risk being particularly high in people with low education. However, the effect of education on age-related cognitive changes remains controversial [40]. Kremen et al. [41] sought

to demonstrate that the impact of CR factors is primarily downstream of intellectual capacity. These researchers concluded that brain development is substantial during childhood and adolescence and that further education from the age of 20 years would contribute much less to brain development. Moreover, it should be considered that the quality of the educational experience is not the same for all individuals, which may influence its potential impact as a CR proxy.

The protective effect of education not only mediates the transition between normal and pathological aging but also between stages of cognitive impairment. Based on the hypothesis that less automatized cognitive domains (or those that did not achieve proper consolidation throughout life) may deteriorate sooner than more consolidated ones, a recent retrospective study aimed to investigate whether education modifies the profile of cognitive/executive performance (i.e., sustained and divided attention, inhibitory control, working memory, verbal, motor and graphomotor fluency, planning, abstract reasoning, and episodic memory) in Mild Cognitive Impairment (MCI). It was found that despite a similar pattern of cognitive decline in both higher and lower education groups, patients with higher education revealed a trend toward a higher proportion of abnormal performances (≤ -1.5 standard deviation on age- and education-adjusted normative scores) and a steeper decline in measures of sustained attention and episodic memory [42]. These findings suggest that patients with higher levels of education have a higher CR because they show a more pronounced decline in executive control that does not reflect differences in clinical disease staging [35, 43, 44]. On the opposite extreme of educational level, elderly illiterate subjects may be more vulnerable to cognitive decline and dementia, due to the lack of the protective effect of education [45–49].

It is worth noting that, although education is usually measured by the number of years of formal education, there may be other indicators that better capture its true impact. In a recent prospective longitudinal cohort study on aging and cognition, which recruited and followed 275 healthy community subjects seen in primary care settings, with 50 years or older, over a 5-year period, investigators found that being male, older, and with a lower age- and education-adjusted z-scores on divided attention/mental flexibility measures were significant independent predictors of cognitive impairment 5 years later. Moreover, vocabulary emerged as a stronger predictor of cognitive stability or decline than education, independently of their correlation [50]. This highlights the relevance of this measure by reflecting more accurately the degree of cognitive stimulation and intellectual enrichment that may account for subtle differences between subjects at the same educational level, particularly relevant in overall low-literacy populations.

Occupational and leisure activities may also have markedly significant protective effects on cognitive decline and dementia, especially for individuals whose jobs involve social interaction [51]. In fact, it is known that engagement in mentally stimulating activities throughout life may promote neural connectivity [52]. With respect to occupational activity, cognitively demanding work conditions are associated with a decreased risk of cognitive decline in older adults [53]. Middle-aged people at risk for AD (decreased hippocampal volume and increased brain atrophy) with greater occupational complexity (e.g., involving complex social interactions) maintained a similar level of cognitive performance as those with less pathology [51, 54]. However, since higher levels of education are usually associated with jobs that are more cognitively demanding, whether or not the protective effect of education is independent of the levels of work complexity in middle age remains controversial [55, 56]. Moreover, a synergistic effect of low education and occupation on the risk of developing AD

was described by Stern et al. [57], particularly when it is combined with cognitively demanding work activity in adulthood [55, 57]. For instance, some studies indicate that level of literacy is a more accurate measure of CR than years of education [58], especially in those individuals from disadvantaged groups or with null/low educational attainment [39, 59]. Regarding involvement in leisure activities, it has also been associated with a reduced risk of AD [60, 61] and protective effects against cognitive decline [62, 63].

There seems to be evidence that lifestyle and the environment effectively regulate cognitive aging and that this regulation may be particularly relevant in the hippocampal-mediated memory functions in mammals. Although the causal nature of this relationship has not yet been established [64], studies in animal models seem to indicate that it may exist, but more clinical studies are needed to specifically understand how social involvement and integration can be used to prevent cognitive decline. Additionally, the mechanisms underlying this relationship seem to indicate a relevant role for growth factors, neuroinflammation, and neurogenesis processes. In this context, physical activity, for instance, has been identified as inducing neurogenesis due to its benefits on structural and functional plasticity in hippocampus-dependent learning and memory tasks. Accordingly, maintaining an active social life at older ages can improve CR and benefit cognitive function. This is especially relevant since some aspects, such as education or occupational complexity, developed at a young age and middle age cannot be modified. Social activity can contribute to an increased reserve even in a more advanced stage of life, with gains in cognitive performance. In fact, living alone was significantly associated with an increase in cognitive complaints and a significant predictor of future cognitive decline in specific linguistic/executive measures, such as verbal fluency over a 5-year follow-up [33, 65, 66]. Social interactions can be viewed as natural forms of cognitive stimulation and may play a relevant part in the stimulation of language skills, whereas living alone would represent a relative cognitive deprivation situation, with reduced cognitive stimulation and lower CR [67, 68]. Interventions that reduce social isolation at a more advanced stage can benefit cognitive function both directly and indirectly by building reserve, especially in individuals with low CR in middle age. This aspect has important implications for interventions suggesting that combating social isolation can contribute to a healthier cognition [69].

3. Compensatory mechanisms of CR and EF

Traditionally, late-mature regions, such as the frontal lobes, are considered especially vulnerable to normal age changes, inspiring theories of cognitive aging, such as the "last in, first-out" or "retrogenesis" hypothesis. This hypothesis considers an anteroposterior gradient of age vulnerability, which explains the decline in EF often observed in healthy older adults [70].

Executive functions, such as processing speed, working memory, inhibitory control, top–down suppression, or shifting ability, are shaped by education and by other CR proxies. A decline in executive performance has been shown to be associated with low performance in activities of daily living and to predict conversion from MCI to dementia [71, 72]. Moreover, EF are known to be sensitive to damage in other parts of the brain, such as subcortical white matter changes [34], thalamic nuclei, the limbic system, and basal ganglia [73] apart from prefrontal lobe damage.

The perspective that age-related cognitive decline emerges when a person is no longer able to compensate for the reduced functioning of the primary brain structures and circuits, is largely supported in the literature. Relevant conceptual models have emerged over the last 20 years, aiming to describe and understand brain reorganization in response to age-related changes and brain injury. Older adults may use alternative networks to aim for the same level of functioning as younger individuals, which can represent a mechanism of neural compensation [74, 75]. The "Scaffolding Theory of Aging and Cognition" (STAC) model proposed by Park and Reuter-Lorenz [76] claims the recruitment of additional circuits as a way to strengthen the declining structures whose functioning has become inefficient. These strategies lose efficiency in the aged brain and are eventually no longer accessible when there is cerebral pathology, as in the case of AD. The "normalcy-pathology homology" phenomenon suggests that there are regions more vulnerable to age-related changes and that this age vulnerability renders them more susceptible to additional pathological AD-related changes. This is particularly clear in frontotemporal regions where the elderly, even with a low risk of AD, present prominent cortical reductions [70].

The Cognitive Reserve framework suggests that individual differences in cognitive performance are based on more efficient recruitment of brain networks (neural reserve) or the enhanced ability to recruit alternate (compensation) brain networks [15, 77]. Regarding neural reserve, it is postulated that inter-individual variability related to the efficiency, capacity, or flexibility of the brain networks will influence how the healthy brain can deal with the demands imposed by the emergence of brain injuries or pathologies. The neural reserve allows healthy young individuals with greater CR to solve tasks more efficiently and more capably and, in turn, may better confront the disruptions imposed by brain pathology due to the increased flexibility of brain networks. Neural compensation concerns task-related activation, a mechanism that only appears when new resources are needed to maintain or improve performance due to changes in the brain structure. Hence, neural compensation is a mechanism usually referring to people who have brain pathology [15, 77]. The degree of compensation can also vary in individuals in terms of expression and effectiveness. In fact, neural compensation refers to inter-individual variability to compensate for the disruption of standard processing networks. In this situation, brain structures or networks that are not normally used by individuals with intact brains become activated. Both neural reserve and neural compensation support CR, with compensation being the most common mechanism in more advanced stages of the aging spectrum [78].

As previously stated, individuals with higher CR can maintain a more efficient and capable network or compensate advantageously in the face of a comparable amount of brain pathology [79]. Accordingly, Scarmeas et al. [80], using a set of memory tasks, identified brain regions where systematic relationships between CR and brain activation differed as a function of aging. Thus, when facing certain tasks, young and older people activate similar brain regions but as the difficulty of the memory task increased the magnitude of activation was often higher in older individuals, suggesting more efforts to achieve a comparable level of performance, which can be related to network efficiency. In addition, the older adults recruited additional regions of the brain not used by young people while performing certain memory tasks, which can represent a form of active neural compensation [80]. A similar pattern of compensation was also found when comparing old adults schooled later in life with old adults schooled at the proper age, in a memory recognition task using Magnetoencephalography (MEG), and the first ones displayed additional activations to keep the level of performance [81].

In the last few decades, scientific studies have tried to capture the "neural implementation" of CR through functional neuroimaging [78]. This approach seeks to identify resting state or task-related functional activation brain networks that may underlie CR. Potentially, the expression of these networks may be associated with the influence of CR proxies, moderating the effect of brain changes on cognition. If these networks were identified through functional neuroimaging research methods (not properly used in clinical practice), their degree of manifestation would be a more direct measure of CR than other types of proxies [17]. Tucker and Stern [37] suggested that there may be at least one "generic CR network" that can be activated during the performance of many tasks, explaining how CR protects against brain pathology, which seems to be a promising line of future investigation [17].

A recent systematic review indicates that a resting-state network, implicating medial temporal regions and cingulate cortex (anterior or posterior), is associated with neural reserve, whereas frontal regions and the dorsal attentional network (DAN), activated during the cognitive engagement, are related to neural compensation [78]. Task-related studies have found a positive correlation between CR proxies (mostly premorbid IQ and education) and higher frontal activity in healthy older adults compared to young adults [82–85]. Moreover, a positive association between CR (i.e., education-occupation attainment, premorbid IQ, and leisure activities) and frontal activity in MCI and AD patients compared to healthy older adults has been found [86, 87].

The mechanisms on which the function and resilience of large-scale brain networks are based are still poorly understood. Early lifespan environmental influences can contribute to understanding phenomena such as reserve, as, at least partially, to determine the variance of the underlying structural network. This may have implications for global and regional network controllability. A dynamic network theory can be crucial for advancing the understanding of the resilience of the human brain, reinforcing the need for a spatiotemporal analysis in complex systems [88]. In fact, the human capacity to perform a variety of tasks seems to be associated with cognitive control networks, specifically the frontoparietal control network (FPN) in the left posterior parietal cortex. The adaptability of this network, whose global connectivity pattern seems to change more than other networks, and the connectivity patterns that can be used to identify task performance, point to the importance of this network in cognitive control and task performance. It seems to be possible through "flexible hubs," that is, regions that quickly update their connectivity pattern according to task demands [89].

This greater variability in FPN connectivity, both between networks and between tasks, supports the notion that this network implements core flexible hubs, allowing cognitive control across various and distinct tasks [89]. This is especially relevant for this chapter's purpose as the existence of this control network appears to be crucial for reserve. Specifically, one of its hubs, the left frontal cortex (LFC, covering BA 6/44) [90, 91], is a likely candidate for the neural implementation of CR. The resting-state connectivity of that LFC hub region had previously been associated with protective factors such as high IQ and high cognitive performance. Concretely, it had already been demonstrated that the lateral prefrontal cortex (LPFC) is a hub region with an especially high global connectivity but, more than that, it has been shown that this global connectivity could predict the fluid intelligence of individuals, appearing to be a global hub connector [92]. This level of the organization thus appears to be especially relevant for understanding the brain and CR that involve distributed circuits and complex psychological constructs.

Global connectivity of the LFC hub (close to the Broca area), in resting-state fMRI, is associated with more years of education (CR proxy) and with milder effects of FDG-PET hypometabolism on memory performance in prodromal AD [91]. This can be important for instance in the selection of participants for intervention trials since MCI patients with higher CR seem to have a higher likelihood to benefit from a cognitive intervention [93].

Increased frontoparietal activation may reflect a compensatory mechanism, helping to protect memory task performance in early-stage AD. Additionally, increased global connectivity of LFC can support frontoparietal increased activation and that is associated with CR, moderating the association between AD neuropathology and cognitive decline, and helping to maintain better memory performance [90]. In a task-related fMRI study, the authors tried to understand if LFC hub connectivity during an episodic memory task was associated with a reserve in aging and MCI. More years of education were associated with increased LFC connectivity during memory processing, and increased LFC connectivity was associated with a higher reserve in the memory domain. This result pattern was found in controls and MCI groups, which was interpreted as suggestive that connectivity of a key hub of the frontoparietal control network contributes to reserve in both normal and pathological aging. This conclusion reinforces that LFC is a good candidate for the neural basis of reserve and that a higher LFC connectivity may be a long-lasting trait that is influenced by environmental stimuli, namely education [91]. In fact, CR, being the result of multiple and distinct stimulations, involves connectivity between different tasks and domains. Consistently with this, the LFC (BA 6/44) ranks among the top 5% of brain regions in terms of number of connections in the brain, being high and globally connected to the rest of the brain and is a key connector hub between different functional networks [91]. Taken together the results seem to point out that the cognitive control network, particularly LFC, works as a hub of the frontoparietal control network, which is associated with greater reserve. Later work showed that education is associated with better performance on memory tasks thanks to greater efficiency of functional networks, clearly demonstrating the effects of education on DMN/DAN small-worldness, mediated via LFC connectivity, and reinforcing its role as a neural basis of the reserve [94].

Moreover, evidence also shows that education facilitates the brain's ability to form segregated functional groups of networks, with stronger signals in parietal and occipital regions [95]. This fact reinforces the perspective that more years of schooling trigger a more specialized use of neural processing. However, CR (residual variance in memory and general executive functioning) was also associated with higher global network efficiency (i.e., functional integration). In this sense, this study corroborates that CR is associated both with increased functional connectivity and better organization of the network topology.

The protective role of higher global functional connectivity in the FPN and higher local connectivity between the salience network (anterior cingulate cortex) and medial frontal cortex can significantly mitigate the impact of white matter lesions on EF [96], emphasizing the role of the cognitive control network as a neural substrate for CR. As pointed out by the authors, both the salience and the FPN are important cognitive control networks, that are crucial for appropriate brain functioning, with the FPN flexibly regulating the activity of other networks and the salience network integrating inputs from different sources. Their results reinforce the notion that cognitive control networks may play a role in brain resilience mechanisms with increased connectivity being linked to better cognition.

Overall, these findings suggest that greater activity of frontal regions, namely via LFC connectivity, is a potential component of functional networks underlying neural compensation. Conversely, MTL regions, which are known to be critical for the conversion from MCI to AD, may reflect the capacity of the neural reserve [97, 98].

4. Conclusions

The understanding of the mechanisms involved with successful aging is far from straightforward and the growing number of publications in this field shows the interest of the scientific community to understand the importance of complex related concepts in its promotion. In this chapter, we focused on several socio-behavioral CR proxies identified as protective factors against cognitive decline and dementia and how they impact EF by means of neural compensation mechanisms related to the increased functional activity of the frontal lobe.

The relationship between CR proxies and the maintenance of cognitive efficiency in the context of age-related changes/brain pathology is dynamic. Not only do the skills, social involvement, and occupational attainment developed throughout life have a mediating role in improving neural connections (i.e., in terms of activation, flexibility, and efficiency), but also this enhancement of brain connectivity patterns expresses itself in better cognitive performance. Despite its vulnerability to the effects of senescence, the frontal lobes play a key role in CR allowing for the preservation of the overall cognitive function by means of enrichment of EF (e.g., planning, sequencing, inhibitory control, abstract reasoning) via a higher CR. Indeed, people with high CR show an advantage in the use of these more developed EF, thus increasing frontal lobe activity. The use of alternative task-relevant circuits compensates for effectiveness (e.g., MTL, especially relevant for memory and selectively affected in AD) thus mitigating the clinical expression of dementia. In this compensation mechanism, DAN and FPN networks are particularly relevant, with a sub-region in the LFC being identified as a potential candidate for a neural marker of CR.

Several caveats still, however, need to be fully addressed. First and foremost, it is unclear how CR proxies may specifically influence different aetiologies of dementia and modulate different cognitive trajectories. Second, EF cannot have a double role as an age−/pathology-dependent measure and as a factor that changes the relationship. As a consequence, all EF may not be appropriate measures for CR, since it is not stable throughout life and is vulnerable to age-related changes. Thus, according to the gain/loss hypothesis, one should carefully select aspects of EF that are robust and resistant to aging, in order to include them as components of CR. Stern et al. [99] considered that this approach should be better explored in the future, despite currently presenting some limitations that are difficult to overcome. From the outset, the fact that the brain measures used to predict cognition only partially capture brain pathology or physiology and different lifestyles cannot be explained by known brain predictors can lead to a high risk of including many aspects that are not reserved. Third, the differential impact of CR depending on the demographic characteristics of the population or discrepancies in measuring CR measures or outcomes (i.e., cognitive or functional) needs to be addressed as well. In fact, precise operational definitions of CR and other related theoretical constructs are needed. Advances in multimodal imaging, preferably longitudinal studies, will allow a better understanding of the neural mechanisms underlying CR. Future work should focus on the design of studies that will help to clarify the relationship between CR proxies

and brain reserve, as well as improve their measurement. These studies will make it possible to improve and integrate the existing conceptual models of the moderation of CR in cognitive performance. Further, it is expected that the contribution of these investigations could lead to objective guidelines and strategies for the development of differentiated, validated, and accessible intervention programs aimed to provide more functionality and better quality of life in older adults [17].

If the existence of a compensatory capacity in individuals with a high CR seems to be clear, it is consensual that it is still not entirely clear what reserve consists of in neural terms. Potential candidates have been proposed but the discovery of this neural basis is particularly relevant as, in addition to traditional cognitive and psychosocial stimulation techniques, it could also open doors to more direct brain stimulation allowing the use of a whole arsenal of new non-invasive brain stimulation technologies which is predicted to have increasing importance in intervention.

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References

[1] GBD 2019 Dementia Forecasting Collaborators. Estimation of the global prevalence of dementia in 2019 and forecast prevalence in 2050: An analysis for the global burden of disease study 2019. The Lancet Public Health. 2022;**00249-8**(1):S2468-S2667. DOI: 10.1016/S2468-2667(21)00249-8

[2] Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. Lancet. 2017;**390**(10113):2673-2734. DOI: 10.1016/S0140-6736(17)31363-6

[3] Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the lancet commission. Lancet. 2020;**396**(10248):413-446. DOI: 10.1016/S0140-6736(20)30367-6

[4] Morris MC, Tangney CC, Wang Y, Sacks FM, Bennett DA, Aggarwal NT. MIND diet associated with reduced incidence of Alzheimer's disease. Alzheimer's & Dementia. 2015;**11**(9):1007-1014. DOI: 10.1016/j.jalz.2014.11.009

[5] Zheng G, Xia R, Zhou W, Tao J, Chen L. Aerobic exercise ameliorates cognitive function in older adults with mild cognitive impairment: A systematic review and meta-analysis. British Journal of Sports Medicine. 2016;**50**(23):1443-1450. DOI: 10.1136/bjsports-2015-095699

[6] Sachdev PS, Lipnicki DM, Crawford J, Reppermund S, Kochan NA, Trollor JN, et al. Factors predicting reversion from mild cognitive impairment to normal cognitive functioning: A population-based study. PLoS One. 2013;**8**(3):e59649. DOI: 10.1371/journal.pone.0059649

[7] Arenaza-Urquijo EM, Wirth M, Chételat G. Cognitive reserve and lifestyle: Moving towards preclinical Alzheimer's disease. Frontiers in Aging Neuroscience. 2015;**7**:134. DOI: 10.3389/fnagi.2015.00134

[8] Vemuri P, Lesnick TG, Przybelski SA, Machulda M, Knopman DS, Mielke MM, et al. Association of lifetime intellectual enrichment with cognitive decline in the older population. JAMA Neurology. 2014;**71**(8):1017-1024. DOI: 10.1001/jamaneurol.2014.963

[9] Willey JZ, Gardener H, Caunca MR, Moon YP, Dong C, Cheung YK, et al. Leisure-time physical activity associates with cognitive decline: The northern Manhattan study. Neurology. 2016;**86**(20):1897-1903. DOI: 10.1212/WNL.0000000000002582

[10] Arenaza-Urquijo EM, Vemuri P. Resistance vs resilience to Alzheimer disease: Clarifying terminology for preclinical studies. Neurology. 2018;**90**(15):695-703. DOI: 10.1212/WNL.0000000000005303

[11] Montine TJ, Cholerton BA, Corrada MM, Edland SD, Flanagan ME, Hemmy LS, et al. Concepts for brain aging: Resistance, resilience, reserve, and compensation. Alzheimer's Research & Therapy. 2019;**11**(1):22. DOI: 10.1186/s13195-019-0479-y

[12] Álvares Pereira G, Nunes MVS, Alzola P, Contador I. Cognitive reserve and brain maintenance in aging and dementia: An integrative review. Applied Neuropsychology. Adult. 2021:1-11. DOI: 10.1080/23279095.2021.1872079

[13] Anonymous. Reserve capacity of the brain. British Medical Journal. 1940;**2**(4167):673-674

[14] Katzman R, Terry R, DeTeresa R, Brown T, Davies P, Fuld P, et al. Clinical, pathological, and neurochemical changes in dementia: A subgroup with preserved mental status and numerous neocortical plaques. Annals of Neurology. 1988;**23**(2):138-144. DOI: 10.1002/ana.410230206

[15] Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. Journal of the International Neuropsychological Society. 2002;**8**(3):448-460. DOI: 10.1017/S1355617702813248

[16] Satz P. Brain reserve capacity on symptom onset after brain injury: A formulation and review of evidence for threshold theory. Neuropsychology. 1993;**7**(3):273-295. DOI: 10.1037/0894-4105.7.3.273

[17] Stern Y, Arenaza-Urquijo EM, Bartrés-Faz D, Belleville S, Cantilon M, Chételat G, et al. Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. Alzheimer's & Dementia. 2020;**16**(9):1305-1311. DOI: 10.1016/j.jalz.2018.07.219

[18] Stern Y. Cognitive reserve. Neuropsychologia. 2009;**47**(10): 2015-2028. DOI: 10.1016/j.neuropsychologia.2009.03.004

[19] Nilsson J, Lövdén M. Naming is not explaining: Future directions for the "cognitive reserve" and "brain maintenance" theories. Alzheimer's Research & Therapy. 2018;**10**:34. DOI: 10.1186/s13195-018-0365-z

[20] Buckner RL. Memory and executive function in aging and AD: Multiple factors that cause decline and reserve factors that compensate. Neuron. 2004;**44**(1):195-208. DOI: 10.1016/j.neuron.2004.09.006

[21] Raz N, Lindenberg U, Rodrigue KM, Kennedy KM, Head D, Williamson A, et al. Regional brain changes in aging healthy adults: General trends, individual differences and modifiers. Cerebral Cortex. 2005;**15**(11):1676-1689. DOI: 10.1093/cercor/bhi044

[22] Oosterman JM, Jansen MG, Scherder EJA, Kessels RPC. Cognitive reserve relates to executive functioning in the old-old. Aging Clinical and Experimental Research. 2021;**33**(9):2587-2592. DOI: 10.1007/s40520-020-01758-y

[23] Bennett DA, Wilson RS, Schneider JA, Evans DA, Mendes de Leon CF, Arnold SE, et al. Education modified the relation of AD pathology to level of cognitive function in older persons. Neurology. 2003;**60**(12):1909-1915. DOI: 10.1212/01.wnl.0000069923.64550.9f

[24] EClipSE Collaborative Members, Brayne C, Ince PG, Keage HAD, IG MK, Matthews FE, et al. Education, the brain and dementia: Neuroprotection or compensation? Brain. 2010;**133**(Pt8): 2210-2216. DOI: 10.1093/brain/awq185

[25] Brickman AM, Muraskin J, Zimmerman ME. Structural neuroimaging in Alzheimer's disease: Do white matter hyperintensities matter? Dialogues in Clinical Neuroscience. 2009;**11**(2):181-190. DOI: 10.31887/DCNS.2009.11.2/ambrickman

[26] Schmidt R, Schmidt H, Haybaeck J, Loitfelder M, Weis S, Cavalieri M, et al. Heterogeneity in age-related white matter changes. Acta Neuropathologica. 2011;**122**(2):171-185. DOI: 10.1007/s00401-011-0851-x

[27] Sundermann EE, Biegon A, Rubin LH, Lipton RB, Mowery W, Landau S, et al. Better verbal memory in women than men in MCI despite

similar levels of hippocampal atrophy. Neurology. 2016;**86**(15):368-1376. DOI: 10.1212/WNL. 0000000000002570

[28] Farina M, Paloski LH, Oliveira CR, Argimon IIL, Irigaray TQ. Cognitive reserve in elderly and its connection with cognitive performance: A systematic review. Ageing International. 2018;**43**(4):496-597. DOI: 10.1007/s12126-017-9295-5

[29] Chapko D, McCormack R, Black C, Staff R, Murray A. Life-course determinants of cognitive reserve (CR) in cognitive aging and dementia—A systematic literature review. Aging & Mental Health. 2018;**22**(8):915-926. DOI: 10.1080/13607863.2017.1348471

[30] Chen Y, Lv C, Li X, Zhang J, Chen K, Liu Z, et al. The positive impacts of early-life education on cognition, leisure activity, and brain structure in healthy aging. Aging. 2019;**11**(14):4923-4942. DOI: 10.18632/aging.102088

[31] Harrison TM, Maass A, Baker SL, Jagust WJ. Brain morphology, cognition, and beta-amyloid in older adults with superior memory performance. Neurobiology of Aging. 2018;**67**:162-170. DOI: 10.1016/j.neurobiolaging.2018.03.024

[32] Chapko D, McCormack R, Black C, Staff R, Murray A. Life course determinants of cognitive reserve (CR) in cognitive aging and dementia—A systematic literature revie. Aging and Mental Health. 2017;**13**:1-12. DOI: 10.1080/13607863.2017.1348471

[33] Martins IP, Maruta C, Silva C, Rodrigues P, Chester C, Ginó S, et al. The effect of education on age-related changes in three cognitive domains: A cross-sectional study in primary care. Applied Neuropsychology: Adult. 2012;**19**(4):287-298. DOI: 10.1080/09084282.2012.670145

[34] Martins IP, Maruta C, Freitas V, Mares I. Executive performance in older Portuguese adults with low education. The Clinical Neuropsychologist. 2013;**27**(3):410-425. DOI: 10.1080/13854046.2012.748094

[35] Sundermann EE, Biegon A, Rubin LH, Lipton RB, Mowrey W, Landau S, et al. Better verbal memory in women than men in MCI despite similar levels of hippocampal atrophy. Neurology. 2016;**86**(15):1368-1376. DOI: 10.1212/WNL.0000000000002570

[36] Salthouse TA. Mental exercise and mental aging: Evaluating the validity of the "use it or lose it" hypothesis. Perspectives on Psychological Science. 2006;**1**(1):68-87. DOI: 10.1111/j.1745-6916.2006.00005.x

[37] Tucker AM, Stern Y. Cognitive reserve in aging. Current Alzheimer Research. 2011;**8**(4):354-360. DOI: 10.2174/156720511795745320

[38] 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**(6):e38268. DOI: 10.1371/journal.pone.0038268

[39] Contador I, Bermejo-Pareja F, Del Ser T, Benito-León J. Effects of education and word reading on cognitive scores in a community-based sample of Spanish elders with diverse socioeconomic status. Journal of Clinical and Experimental Neuropsychology. 2015;**37**(1):92-101. DOI: 10.1080/13803395.2014.989819

[40] Seblova D, Berggren R, Lövdén M. Education and age-related decline in cognitive performance: Systematic review and meta-analysis of longitudinal

cohort studies. Ageing Research Reviews. 2020;**58**:101005. DOI: 10.1016/j.arr.2019.101005

[41] Kremen WS, Beck A, Elman JA, Gustavson DE, Reynolds CA, Tu XM, et al. Influence of young adult cognitive ability and additional education on later-life cognition. Proceedings of the National Academy of Sciences of the United States of America. 2019;**116**(6):2021-2026. DOI: 10.1073/pnas.1811537116

[42] Godinho F, Maruta C, Borbinha C, Pavão MI. Effect of education on cognitive performance in patients with mild cognitive impairment. Applied Neuropsychology. Adult. 2021;**15**:1-10. DOI: 10.1080/23279095.2021.1887191

[43] Scarmeas N, Stern Y, Mayeux R, Luchsinger JA. Mediterranean diet, Alzheimer disease, and vascular mediation. Archives of Neurology. 2006;**63**(12):1709-1717. DOI: 10.1001/archneur.63.12.noc60109

[44] Wilson RS, Li Y, Aggarwal NT, Barnes LL, McCann JJ, Gilley DW, et al. Education and the course of cognitive decline in Alzheimer disease. Neurology. 2004;**63**(7):1198-1202. DOI: 10.1212/01.wnl.0000140488.65299.53

[45] Brayne C, Ince PG, Keage HAD, McKeith IG, Matthews FE, Polvikoski T, et al. Education, the brain and dementia: Neuroprotection or compensation? EClipSE Collaborative Members. Brain. 2010;**133**(8):2210-2216. DOI: 10.1093/brain/awq185

[46] Brickman AM, Siedlecki KL, Muraskin J, Manly JJ, Luchsinger JA, Yeung L-K, et al. White matter hyperintensities and cognition: Testing the reserve hypothesis. Neurobiology of Aging. 2011;**32**(9):1588-1598. DOI: 10.1016/j.neurobiolaging.2009.10.013

[47] Koepsell TD, Kurland BF, Harel O, Johnson EA, Zhou XH, Kukull WA. Education, cognitive function, and severity of neuropathology in Alzheimer disease. Neurology. 2008;**70**(19 Pt 2):1732-1739. DOI: 10.1212/01.wnl.0000284603.85621.aa

[48] Lane EM, Paul RH, Moser DJ, Fletcher TD, Cohen RA. Influence of education on subcortical hyperintensities and global cognitive status in vascular dementia. Journal of the International Neuropsychological Society. 2011;**17**(3):531-536. DOI: 10.1017/S1355617711000324

[49] Valenzuela MJ, Sachdev P. Brain reserve and dementia: A systematic review. Psychological Medicine. 2006;**36**(4):441-454. DOI: 10.1017/S0033291705006264

[50] Martins IP, Maruta C, Morgado J, Loureiro C, Tavares J, Freitas V, et al. Predictors of cognitive stability or decline during aging: A longitudinal study in primary care. Applied Neuropsychology: Adult. 2020;**27**(1):22-34. DOI: 10.1080/23279095.2018.1476866

[51] Boots EA, Schultz SA, Almeida RP, Oh JM, Koscik RL, Dowling MN, et al. Occupational complexity and cognitive reserve in a middle-aged cohort at risk for Alzheimer's disease. Archives of Clinical Neuropsychology. 2015;**30**(7):634-642. DOI: 10.1093/arclin/acv041

[52] Serra L, Bruschini M, Di Domenico C, Gabrielli GB, Marra C, Caltagirone C, et al. Memory is not enough: The neurobiological substrates of dynamic cognitive reserve. Journal of Alzheimer's Disease. 2017;**58**(1):171-184. DOI: 10.3233/JAD-170086

[53] Then FS, Luck T, Luppa M, Arélin K, Schroeter ML, Engel C, et al. Association between mental demands at work and cognitive functioning in the general population—Results of the health study of the Leipzig research center for civilization diseases (LIFE). Journal of Occupational Medicine and Toxicology. 2014;**9**:23. DOI: 10.1186/1745-6673-9-23

[54] Kröger E, Andel R, Lindsay J, Benounissa Z, Verreault R, Laurin D. Is complexity of work associated with risk of dementia? The Canadian study of health and aging. American Journal of Epidemiology. 2008;**167**(7):820-830. DOI: 10.1093/aje/kwm382

[55] Dekhtyar S, Wang H-X, Scott K, Goodman A, Koupil I, Herlitz A. A life-course study of cognitive reserve in dementia—From childhood to old age. The American Journal of Geriatric Psychiatry. 2015;**23**(9):885-896. DOI: 10.1016/j.jagp.2015.02.002

[56] Karp A, Andel R, Parker MG, Wang HX, Winblad B, Fratiglioni L. Mentally stimulating activities at work during midlife and dementia risk after age 75: Follow-up study from the Kungsholmen project. The American Journal of Geriatric Psychiatry. 2009;**17**(3):227-236. DOI: 10.1097/JGP.0b013e318190b691

[57] Stern Y, Gurland B, Tatemichi TK, Tang MX, Wilder D, Mayeux R. Influence of education and occupation on the incidence of Alzheimer's disease. Journal of the American Medical Association. 1994;**271**(13):1004-1010

[58] Baldivia B, Andrade VM, Bueno OFA. Contribution of education, occupation and cognitively stimulating activities to the formation of cognitive reserve. Dementia & Neuropsychologia. 2008;**2**(3):173-182. DOI: 10.1590/S1980-57642009DN20300003

[59] Whalley LJ, Staff RT, Fox HC, Murray AD. Cerebral correlated of cognitive reserve. Psychiatry Research: Neuroimaging. 2016;**247**:65-70. DOI: 10.1016/j.pscychresns.2015.10.012

[60] Scarmeas N, Levy G, Tang MX, Manly J, Stern Y. Influence of leisure activity on the incidence of Alzheimer's disease. Neurology. 2001;**57**(12):2236-2242. DOI: 10.1212/wnl.57.12.2236

[61] Verghese J, Lipton RB, Katz MJ, Hall CB, Derby CA, Kuslansky G, et al. Leisure activities and the risk of dementia in the elderly. The New England Journal of Medicine. 2003;**348**(25):2508-2516. DOI: 10.1056/NEJMoa022252

[62] Ribeiro AM, Monteiro S, Pereira AS. Leisure activities as a predictor of cognitive decline and dementia in old age. Open Journal of Social Sciences. 2017;**5**(3):254-259. DOI: 10.4236/jss.2017.53023

[63] Wang H-X, Jin Y, Hendrie HC, Liang C, Yang L, Cheng Y, et al. Late life leisure activities and risk of cognitive decline. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2013;**68**(2):205-213. DOI: 10.1093/gerona/gls153

[64] Dause TJ, Kirby ED. Aging gracefully: Social engagement joins exercise and enrichment as a key lifestyle factor in resistance to age-related cognitive decline. Neural Regeneration Research. 2019;**14**:39-42. DOI: 10.4103/1673-5374.243698

[65] Martins IP, Mares I, Stilwell PA. How subjective are subjective language complaints. European Journal of Neurology. 2012;**19**:666-671. DOI: 10.1111/j.1468-1331.2011.03635.x

[66] Maruta C, Martins IP. May subjective language complaints predict future

language decline in community-dwelling subjects? Frontiers in Psychology. 2019;**10**:1974. DOI: 10.3389/fpsyg.2019.01974

[67] Bennett DA, Schneider JA, Tang Y, Arnold SE, Wilson RS. The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: A longitudinal cohort study. Lancet Neurology. 2006;**5**:406-412. DOI: 10.1016/S1474-4422(06)70417-3

[68] Gow AJ, Corley J, Starr JM, Deary IJ. Which social network or support factors are associated with cognitive abilities in old age? Gerontology. 2013;**59**:454-463. DOI: 10.1159/000351265

[69] Evans ISEM, Llewellyn DJ, Matthews FE, Woods RT, Brayne C, Clare L, et al. Social isolation, cognitive reserve, and cognition in healthy older people. PLoS One. 2018;**13**(8):e0201008. DOI: 10.1371/journal.pone.0201008

[70] Fjell AM. McEvoy L, Holland D, dale AM, Walhovd KB, Alzheimers's disease neuroimaging initiative. What is normal in normal aging? Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus. Progress in Neurobiology. 2014;**117**:20-40. DOI: 10.1016/j.pneurobio.2014.02.004

[71] Gibbons LE, Carle AC, Mackin RS, Harvey D, Mukherjee S, Insel P, et al. A composite score for executive functioning, validated in Alzheimer's Disease Neuroimaging Initiative (ADNI) participants with baseline mild cognitive impairment. Brain Imaging and Behavior. 2012;**6**(4):517-527. DOI: 10.1007/s11682-012-9176-1

[72] Tabert MH, Manly JJ, Liu X, Pelton GH, Rosenblum S, Jacobs M, et al. Neuropsychological prediction of conversion to Alzheimer disease in patients with mild cognitive impairment. Archives of General Psychiatry. 2006;**63**(8):916-924. DOI: 10.1001/archpsyc.63.8.916

[73] Lezak MD, Howieson DB, Bigler ED, Tranel D. Neuropsychological Assessment. 5th ed. Oxford: Oxford University Press; 2012

[74] Cabeza R. Hemispheric asymmetry reduction in older adults: The HAROLD model. Psychology and Aging. 2002;**17**(1):85-100. DOI: 10.1037//0882-7974.17.1.85

[75] Stern Y, Zarahn E, Hilton HJ, Delapaz R, Flynn J, Rakitin B. Exploring the neural basis of cognitive reserve. Journal of Clinical and Experimental Neuropsychology. 2003;**5**:691-701. DOI: 10.1076/jcen.25.5.691.14573

[76] Park DC, Reuter-Lorenz P. The adaptive brain: Aging and neurocognitive scaffolding. Annual Review of Psychology. 2009;**60**:173-196. DOI: 10.1146/annurev.psych.59.103006.093656

[77] Stern Y. An approach to studying the neural correlates of reserve. Brain Imaging and Behavior. 2017;**11**(2):410-416. DOI: 10.1007/s11682-016-9566-x

[78] Anthony M, Lin F. A systematic review for functional neuroimaging studies of cognitive reserve across the cognitive aging spectrum. Archives of Clinical Neuropsychology. 2018;**33**(8):937-948. DOI: 10.1093/arclin/acx125

[79] Barulli D, Stern Y. Efficiency, capacity, compensation, maintenance, plasticity: Emerging concepts in cognitive reserve. Trends in Cognitive Sciences. 2013;**17**(10):502-509. DOI: 10.1016/j.tics.2013.08.012

[80] Scarmeas N, Zarahn E, Anderson KE, Hilton J, Flynn J, Van Heertum RL, et al. Cognitive reserve modulates functional brain responses during memory tasks: A PET study in healthy young and elderly subjects. NeuroImage. 2003;**19**(3):1215-1227. DOI: 10.1016/s1053-8119(03)00074-0

[81] Silva Nunes MV, Castro-Caldas A, Del Rio D, Maestú F, Ortiz T. The ex-illiterate brain: The critical period, cognitive reserve and HAROLD model. Dementia & Neuropsychologia. 2009;**3**(3):222-227. DOI: 10.1590/S1980-57642009DN30300008

[82] Bartrés-Faz D, Solé-Padullés C, Junqué C, Rami L, Bosch B, Bargalló N, et al. Interactions of cognitive reserve with regional brain anatomy and brain function during a working memory task in healthy elders. Biological Psychology. 2009;**80**(2):256-259. DOI: 10.1016/j.biopsycho.2008.10.005

[83] Springer MV, McIntosh AR, Winocur G, Grady CL. The relation between brain activity during memory tasks and years of education in young and older adults. Neuropsychology. 2005;**19**(2):181-192. DOI: 10.1037/0894-4105.19.2.181

[84] Steffener J, Reuben A, Rakitin BC, Stern Y. Supporting performance in the face of age-related neural changes: Testing mechanistic roles of cognitive reserve. Brain Imaging and Behavior. 2011;**5**(3):212-221. DOI: 10.1007/s11682-011-9125-4

[85] Waiter GD, Fox HC, Murray AD, Starr JM, Staff RT, Bourne VJ, et al. Is retaining the youthful functional anatomy underlying speed of information processing a signature of successful cognitive ageing? An event-related fMRI study of inspection time performance. NeuroImage. 2008;**41**:581-595. DOI: 10.1016/j.neuroimage.2008.02.045

[86] Bosch B, Bartrés-Faz D, Rami L, Arenaza-UrquijoEM, Fernández-EspejoD, Junqué C, et al. Cognitive reserve modulates task-induced activations and deactivations in healthy elders, amnestic mild cognitive impairment and mild Alzheimer's disease. Cortex. 2010;**46**(4):451-461. DOI: 10.1016/j.cortex.2009.05.006

[87] Solé-Padullés C, Bartrés-Faz D, Junqué C, Vendrell P, Rami L, Clemente IC, et al. Brain structure and function related to cognitive reserve variables in normal aging, mild cognitive impairment and Alzheimer's disease. Neurobiology of Aging. 2009;**30**(7):1114-1124. DOI: 10.1016/j.neurobiolaging.2007.10.008

[88] Medaglia JD, Pasqualetti F, Hamilton RH, Thompson-Schill SL, Bassett DS. Brain and cognitive reserve: Translation via network control theory. Neuroscience and Biobehavioral Reviews. 2017;**75**:53-64. DOI: 10.1016/j.neubiorev.2017.01.016

[89] Cole MW, Reynolds JR, Power JD, Repovs G, Anticevic A, Braver TS. Multi-task connectivity reveals flexible hubs for adaptive task control. Nature Neuroscience. 2013;**16**:1348-1355. DOI: 10.1038/nn.3470

[90] Franzmeier N, Araque-Caballero MÁ, Taylor ANW, Simon-Vermot L, Buerger K, Ertl-Wagner B, et al. Resting-state global functional connectivity as a biomarker of cognitive reserve in mild cognitive impairment. Brain Imaging and Behavior. 2017;**11**(2):368-382. DOI: 10.1007/s11682-016-9599-1

[91] Franzmeier N, Duering M, Weiner M, Dichgans M, Ewers M. Alzheimer's Disease Neuroimaging Initiative

(ADNI). Left frontal cortex connectivity underlies cognitive reserve in prodromal Alzheimer disease. Neurology. 2017;**88**(11):1054-1061. DOI: 10.1212/WNL.0000000000003711

[92] Cole MW, Ito T, Braver TS. Lateral prefrontal cortex contributes to fluid intelligence through multinetwork connectivity. Brain Connectivity. 2015;**5**:497-504. DOI: 10.1089/brain.2015.0357

[93] Franzmeier N, Unterauer E, Ewers M, Düring M, Müller C, Ruiescu D, et al. Effects of age, APOE ε4, cognitive reserve and hippocampal volume on cognitive intervention outcome in amnestic mild cognitive impairment. Journal of Alzheimer's Disease. 2016;**6**:1-7. DOI: 10.4172/2161-0460.1000246

[94] Franzmeier N, Düzel E, Jessen F, Buerger K, Levin J, Duering M, et al. Left frontal hub connectivity delays cognitive impairment in autosomal-dominant and sporadic Alzheimer's disease. Brain. 2018;**141**:1186-1200. DOI: 10.1093/brain/awy008

[95] Marques P, Moreira P, Magalhães R, Costa P, Santos N, Zihl J, et al. The functional connectome of cognitive reserve. Human Brain Mapping. 2016;**37**(9):3310-3322. DOI: 10.1002/hbm.23242

[96] Benson G, Hildebrandt A, Lange C, Schwarz C, Köbe T, Sommer W, et al. Functional connectivity in cognitive control networks mitigates the impact of white matter lesions in the elderly. Alzheimer's Research & Therapy. 2018;**10**(1):109. DOI: 10.1186/s13195-018-0434-3

[97] Bozzali C, Cercignani M. The impact of cognitive reserve on brain functional connectivity in Alzheimer's disease. Journal of Alzheimer's Disease. 2015;**44**(1):243-250. DOI: 10.3233/JAD-141824

[98] Lee JC, Kim SJ, Hong S, Kim Y. Diagnosis of Alzheimer's disease utilizing amyloid and tau as fluid biomarkers. Experimental & Molecular Medicine. 2019;**51**:53. DOI: 10.1038/s12276-019-0250-2

[99] Stern Y, Gazes Y, Razlighi Q, Steffener J, Habeck C. A task-invariant cognitive reserve network. NeuroImage. 2018;**178**:36-45. DOI: 10.1016/j.neuroimage.2018.05.033