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WHAT IS THE REAL ROLE OF PREVENTIVE MEDICINE?

Dissertação – Revisão Bibliográfica

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Mestrado Integrado em Medicina – 6º Ano

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Resumo

Dado o aumento da esperança média de vida e, consequentemente, a existência de uma população progressivamente mais envelhecida, a preocupação com a perda da cognição e memória com a idade torna-se cada vez mais relevante num contexto de saúde global. Contudo, a memória estabelece-se como um dos sistemas mais complexos do nosso cérebro e, como tal, o efeito de diferentes fatores no desenvolvimento e remodelação dos seus processos envolventes é ainda pouco conhecido.

O objetivo deste artigo é rever a literatura existente relacionada com a prevenção da perda cognitiva associada à idade, dando ênfase aos processos de envelhecimento que influenciam os sistemas e mecanismos da memória, às teorias neurocognitivas predominantes sobre a sua manutenção e melhoria e, em especial, às intervenções mais abordadas que se apresentem como relevantes na prevenção do seu declínio.

O cérebro e a memória são processos contínuos e dinâmicos, que dependem de diversos fatores e sofrem alterações significativas ao longo da vida, influenciando o seu desempenho em idades mais avançadas. Assim, está cada vez mais demonstrado que a manutenção da plasticidade e da integridade estrutural e funcional do cérebro pode ser o fator determinante para a conservação da memória e da cognição.

Torna-se progressivamente mais evidente que a adoção de um estilo de vida saudável, com uma nutrição e atividade física reguladas e adaptadas com base nas lacunas e especificidades de cada indivíduo, juntamente com algumas intervenções pontuais, como treinos de reabilitação e desenvolvimento cognitivo, combinados ou não com tecnologias de estimulação transcraniana, representam o presente e futuro da prevenção, e até mesmo do tratamento, no campo da perda cognitiva.

Mais investigação será necessária para fundamentar a verdadeira eficácia destas intervenções e fornecer as estratégias precisas sobre como podem ser aplicadas corretamente, com vista a se tornarem medidas concretas para evitar o declínio da memória com o envelhecimento.

Palavras-chave: Memória e Envelhecimento; Perda de Memória; Declínio Cognitivo; Medicina Preventiva; Intervenção; Nutrição; Atividade Física; Treino Cognitivo

Abstract

Given the increase in life expectancy and consequently in the number of aged inhabitants, concerns about memory and cognitive decline are becoming increasingly more relevant in the global health context. However, memory is certainly one of the most complex processes in our brain and, for that reason, the effects of different factors on the development and on the vicissitudes of the memory processes are still hardly known.

Therefore, the aim of this article is to review the existing literature associated with the prevention of age-related cognitive decline, giving emphasis on the aging processes that influence the memory systems and mechanisms, on the existing neurocognitive theories about the maintenance and improvement of the memory throughout the aging and, especially, on the most discussed preventive interventions that may play an important role in the development of age-related memory impairment.

The brain and its memory are continuous, dynamic and factor-dependent processes that suffer significant changes throughout an individual's lifespan, which influence their performance at older ages. For that reason, there is believed that maintaining the integrity and plasticity of the brain could be the crucial determinant for the preservation of memory and cognition.

It is therefore becoming gradually more evident that a full lifestyle nutrition and physical activity plan, with adaptations based on the individual's impairments and specificities, together with some punctual particular interventions like cognitive training and rehabilitation, combined or not with non-invasive brain stimulation, represents the present and the future of prevention, and even treatment, in the cognitive decline field.

However, further research is required in order to substantiate the true effectiveness of these interventions and to provide detailed strategies of how to correctly apply them as concrete measures in the prevention of age-related memory decline.

Key words: Memory and Aging; Memory Impairment; Cognitive Decline; Preventive Medicine; Intervention; Nutrition; Physical Activity; Cognitive Training

Contents

Lists of abbreviations:

AD: Alzheimer's disease; **LTP:** Long-term Potentiation; **LTD:** Long-term Depression; **STAC:** Scaffolding Theory of Aging and Cognition; **MCI:** Mild Cognitive Impairment; **NMDA:** N-methyl-d-aspartate; **AMPA:** α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; **DHEA:** Dehydroepiandrosterone; **DHA:** Docosahexanoic acid; **EPA:** Eicosapentaenoic acid; **NIBS:** Non-Invasive Brain Stimulation; **DBS:** Deep Brain Stimulation

Introduction

One of the main functions of the human brain is to accumulate knowledge over time so that the individual can benefit from experience.[1] This process, known as memory, has an implicit (or non-declarative) and explicit (or declarative) functioning and is commonly divided in two components: working memory and long-term memory. Working memory is the process that is able to encode and retrieve the information collected by the sensorial system while long-term memory has the function of storing the data through several complex models of processing.[2]

Given that memory is a system that is influenced by many factors in its extremely complex neuronal reaction chain, it is natural that it suffers corruption and quality loss throughout the normal aging process. However, this deterioration does not take place in a uniform way throughout the aging progression and, more than that, it has an enormous inter-individual variation. This occurs due to the numerous factors that may affect any of the multiple paths of the memory process and many studies suggest that changes in cognitive function in old age primarily reflect person-specific factors rather than an inevitable developmental process.[3–7]

Much interest exist in faster than average memory performance decline for a certain age group, as it might be indicative of forthcoming diseases such as dementia, like the Alzheimer's disease, which are physiopathologically relatively well described in the literature. However, despite the huge investment in the research of these diseases, currently no truly effective therapy has been established, being merely symptomatic treatments with no disease-modifying drugs yet developed.[8–11]

This fact enhances the evidence that brain maintenance, in cellular, neurochemical, gray and white-matter integrity, and systems activation patterns levels, could characterize a successful memory aging and that a network-based approach directed to this goal, rather than a single target-based approach, may even be more effective for the treatment of cognitive decline.[7,11,12] Moreover, a preventive medicine approach to this theme appears today as one of the main possible solutions for successful memory aging and brain function in later life.

The goal of this article is to review the existing literature associated with the prevention of age-related cognitive decline, giving emphasis on the aging processes that influence the memory systems and mechanisms, on the existing neurocognitive theories about the maintenance and improvement of the memory throughout the aging and, especially, on the most discussed preventive interventions that may play a significant role in the development of age-related memory impairment.

Methods

This review was based on literature search using *MEDLINE – PubMed*, *ScienceDirect* and *APA PsycNET* databases, from the date of database onset until May 30, 2017. The list of searched terms included "memory impairment", "memory loss", "cognitive decline", "aging", "age-related", "prevention", "preventive intervention", and specific terms related to each chapter of this review.

The studies were included or excluded based on the relevance revealed by the title and the abstract. The inclusion criteria included randomized controlled trials or reviews of pharmacologic or non-pharmacologic interventions in adults with normal baseline cognition. As well, studies that investigated pathological forms of cognitive decline, including the development of mild cognitive impairment and progression to dementia, were included. The selected studies were published in English, between 1988 and May 2017, except for a chapter from an historic book written in 1968. The search also included studies found in the references of the analyzed studies.

Memory and Aging

Memory is defined, in a neurological way, as the faculty of the brain which enables it to encode, store and retrieve informational stimuli collected by the sensorial system throughout the experiences lived by the organism.[13] This process is based on two interrelated foundations: firstly, the specific genetically programmed axonal connections that determine which sets of neurons will be responsive to which types of information, and secondly, the modifications in the synaptic strengths of these connections that establish a record of personal experience and enables the gradual accumulation of a knowledge base that is unique for each individual.[1]

Memory Systems

Regarding the first proposition and taking into account the current neurological knowledge, the memory systems are divided into working memory and long-term memory.

Working memory refers to the ability to temporarily maintain and manipulate information that one needs to keep in mind. As it requires active and conscious participation, working memory is an explicit and declarative memory system.[14] There is a common misconception that working memory and short-term memory are synonymous, however the second concept involves just the simple maintenance of information over a short period of time which, together with other brain components like attention and concentration, generates the capacity to actively reorganize and manipulate the information held, forming the working memory.[15,16] Numerous studies have shown that working memory uses a network of cortical and subcortical areas, being probably the main role taken by the dorsolateral prefrontal cortex in the manipulation and update of the information.[17] The network of areas includes posterior brain regions that are linked with prefrontal regions to form a circuit, with many studies suggesting that the left dorsolateral prefrontal cortex is more involved in verbal tasks and the right dorsolateral prefrontal cortex in visuospatial tasks. More difficult tasks involving working memory require bilateral brain activation and an increase in the number of activated brain regions in the prefrontal cortex.[15,18,19]

Although there is a general consensus that working memory is, among the cognitive functions, one of the most sensitive to impairment in older adults, there is disagreement concerning the mechanisms involved, involving three mainly discussed theories. One proposes that the limitation is based on a reduction of attention resources, being the highest attention demanding task the one that shows more impairment[20]; other theory shows that it can be explained by the reduced speed of the cognitive processes that is commonly seen in older adults, stating that slower processing allows more time for working memory contents to decay, therefore reducing effective capacity[21–23]; and finally there exists a one theory that is based on the lack of inhibitory control, which states that the failure to suppress irrelevant information in working memory may effectively reduce its capacity, denying access to the relevant information.[24,25] West[26] also proposed that, as working memory depends to a large degree on the pre-frontal cortex, the region which deteriorates more than other brain regions as we grow old, could be part of the explanation for the decline of working memory and other related cognitive functions.

Even though the mechanisms underlying these age-related deficits are as yet poorly understood, it seems likely that attention, speed of information processing and the ability to inhibit irrelevant information are all important functions for effective performance of many complex cognitive everyday tasks such as decision-making, problem-solving and the planning of goal-directed behaviors, with the effects of such deficits being far-reaching in a person's life.

Regarding long-term memory, it can be divided into several types, namely, episodic, semantic, autobiographical, procedural and prospective memory.

Episodic memory refers to memory for personally experienced events that occur in a particular place and at a particular time. It is the most advanced form of memory, which may be distinctly human, and is ontogenetically the latest to develop. It also appears to be the most susceptible to brain damage and the most affected by normal aging.[15] It is believed that the major anatomical structures involved are the medial temporal lobes, anterior thalamic nucleus, mammillary body, fornix and prefrontal cortex, each one with different relationships in the memory process.[19] The episodic memory problems experienced by older adults may involve deficient encoding, storage, or retrieval processes.[15]

Many of the common everyday memory lapses reported by normal older adults, such as forgetting where they parked their cars, likely involve poor encoding. These kinds of memory failures have generally been attributed to a reduced use of effortful encoding strategies, which depend particularly on prefrontal brain regions, like not giving enough meaning, elaboration or detail to contextual aspects besides the central content of the new information, which makes the memory traces less distinctive and more similar to others, thereby more difficult to retrieve – this is sometimes referred to as a source memory problem.[27] In what concerns the storage problems of episodic memory, consolidation is thought to involve the binding of various aspects of the experience into a composite memory trace. What is believed to fail is the extent to which an event is bound to its spatial and temporal context. This feature critically depends on medial temporal lobe structures, particularly the hippocampus.[15] Although it is clear that retrieval is at least partly dependent on encoding (well-encoded information is easier to retrieve), there are also effortful retrieval processes that appear to be impaired by aging. In some tests, it was demonstrated that recollection, which requires effortful retrieval of episodic detail, is impaired with age, whereas the more automatic judgments of familiarity, more related to encoding, are intact.[28] Evidence from functional neuroimaging and neuropsychological studies suggests that these more strategic retrieval processes depend on the prefrontal cortex, as well as the hippocampus.[29,30]

Semantic memory, which is believed to be stored in a variety of regions in the posterior neocortex, refers to one's store of general knowledge about the world and knowledge of words and concepts. Such information is not tied to the space or time of learning, and its retrieval is generally prefaced with "I know". Normally, aging older adults do not have significant impairments in semantic memory, in fact, their knowledge of the world often exceeds that of young people.[15,31]

Autobiographical memory involves memory for one's personal past and includes memories that are both episodic and semantic in nature and is believed to have a strong emotional association. As previously stated, episodic memory can be affected while semantic memory does not experience significant impairment through aging, which is exposed in the behavior of autobiographical memory throughout time. Levine et al.[32] measured, through autobiographical interviews, younger and older adults recalling events from 5 life periods. He revealed that whereas younger adults were biased toward episodic

details reflecting happenings, locations, perceptions, and thoughts, older adults favored semantic details not connected to a particular time and place. This suggests that although memory for personal semantics is intact in old age, memory for specific episodic or contextual details about one's personal past may be impaired. However there is a probable mechanism of memory transition between these two components which helps the maintenance of the autobiographical knowledge through aging.[15,33]

Procedural memory refers to the ability to learn behavioral and cognitive skills and algorithms that are used at an automatic, unconscious level, belonging to the implicit type of memory. These highly skilled activities are acquired slowly through extensive practice and depend on several brain regions, including the basal ganglia, the supplementary motor area and the cerebellum.[19] Studies show that procedural memory can be spared in patients who have severe deficits of the episodic memory system, such as patients with Korsakoff's syndrome or Alzheimer's disease (AD), or who have undergone surgical removal of the medial temporal lobes, which demonstrates that procedural memory depends on a memory process that is separate and distinct from the episodic memory and semantic memory systems.[34] In general, older adults show normal acquisition of procedural skills in both motor and cognitive domains and retain them across their lifespan. With high levels of expertise there is often little slowing of skilled performance with age as some individual components of the skill may decline.[15]

Prospective memory, in contrast to retrospective memory, is the form of memory that involves remembering to carry out intended actions at an appropriate point of time in the future. Prospective memory tasks are integrated in our lives, including mundane demands like remembering to put the cap back on the toothpaste or remembering to email back a friend, but also activities that are critical to maintaining life, like remembering to take the medication or remembering to carry out safety checks before a long car drive.[35] Some studies comparing groups of people of different ages suggest that there is a continual improvement of prospective memory since childhood but that a decline begins in late adulthood when prospective responding becomes less accurate and slower than in younger adults.[36–38] This type of memory may rely on some aspects of working memory to maintain future intentions over time, and is also likely to involve divided attention, both functions that show age-related deficits. Prospective memory and episodic memory tend not to be correlated and probably depend on different regions of the prefrontal cortex.[15]

Besides working memory, it appears that episodic memory is the main issue in what concerns the memory decline in aging, with prospective memory also having a role in this matter. It seems that the specificity, detail and context – source monitoring – of the information to be encoded, stored and posteriorly retrieved by the older age memory systems may be a critical determinant of the observed age differences.[15,39,40] The ability to bind pieces of information together as a coherent whole is reduced since older adults are also impaired at forming new item-context correct associations.[43,44]

There is also some suggestion that age-related deficits in memory may be reduced because of the emotional content, personal importance or social relevance of the event, meaning that the emotional weight of the encoded memory may be an important variable. Nevertheless, there are also adverse effects related to the humor, negative emotions or stress levels of the individual, as well as the so called memory self-efficacy, which indicates that older people do not have confidence in their own memory performances, leading to poor consequences.[43,44]

Synaptic Strengths

As previously mentioned, the synaptic strengths of an individual's brain play an imperative role in the expression of the memory process. The patterns of the modifications of these connections are acquired thought an individual's experiences, and so, not encoded at the level of the genome and not transmitted through mitosis.[45] As an inevitable outcome of this arrangement, each neuron in the brain becomes exposed to the cumulative effects of biological deterioration throughout the life span.[1]

The mechanism of these neuronal modifications, known as synaptic plasticity, can result, over time, in either a decline in the efficacy of the synapse, called depression, or an improvement, called potentiation. Long-term potentiation (LTP) produces a long-lasting increase in signal transmission between two neurons and is a form of synaptic plasticity that fulfils many of the criteria for a neural correlation of memory and learning. The opposite version is called long-term depression (LTD), which produces a long-lasting decrease in synaptic strength, having also a role in these processes.[46,47]

There are several underlying mechanisms that cooperate to achieve synaptic plasticity, including changes in the quantity of neurotransmitters released into a synapse

and changes in how effectively cells respond to those neurotransmitters.[48] Two well-known molecular mechanisms involve the NMDA and AMPA glutamate postsynaptic receptors. Glutamate binding causes the AMPA receptors to open, which enables the flow of Na^+ into the postsynaptic cell, resulting in a depolarization. NMDA receptors, however, do not open directly because their pores are at the resting membrane's potential conformation, occluded by Mg^{2+} ions. For that to not happen, a strong depolarization lead by the AMPA receptors completely displaces the magnesium ions that block the NMDA ion channels and allows calcium ions to enter the cell. This Ca^{2+} triggers the upregulation of AMPA receptors to the membrane, which results in a long-lasting increase in excitatory postsynaptic potential size, causing LTP. Weaker depolarizations only partially displace the Mg^{2+} ions, resulting in less Ca^{2+} entering the post-synaptic neuron, and so, lower intracellular calcium concentrations. This process then activates protein phosphatases and induce LTD.[49–51] The second mechanism depends on a second messenger cascade regulating gene transcription and changes in the levels of key proteins at synapses such as calcium/calmodulin dependent protein kinase II (CaMKII) and protein kinase AII (PKAII). The activation of the second messenger pathway, with the calcium influx from NMDA receptors, leads to augmented levels of these protein kinases within the dendritic spine, which increases its volume and is linked to LTP processes such as the addition of AMPA receptors to the plasma membrane and phosphorylation of ion channels for enhanced permeability. This is a focal stimulation process and is inactivated before spreading to adjacent spines, enabling particular changes in protein activation to be confined to a single dendritic spine, enhancing their responsivity.[52,53]

Long-lasting modifications in synaptic transmission also depend on the number of presynaptic contacts on dendritic spines. This is improved by increasing the population of spines that are contacted by multiple presynaptic terminals. Also, by changing the cytoskeletal structure of dendritic spines, spines are lengthened and the possibility of synaptic contacts with the axonal terminals of the presynaptic cell is increased. These two processes are modulated by the activin molecule, which is upregulated during the early stage of LTP, and results in long-term maintenance of the potentiation.[54]

It is important to refer that LTD is one of the main processes to selectively weaken specific synapses in order to make constructive use of synaptic strengthening caused by LTP. This is necessary because, if allowed to continue increasing in strength, synapses

would ultimately reach a ceiling level of efficiency, which would inhibit the encoding of new information.[55]

Given that this is a natural outcome, many researchers have suggested that changes in the synaptic function provide a principal physiological correlation of brain aging and memory decline.[56–58]

There are several mechanisms that may possibly contribute to the observed synaptic plasticity age-related impairments, namely loss of synaptic contacts, decreased neurotransmitter release, and reduced postsynaptic responsiveness to the transmitter.[57] This leads to deficits in the induction and maintenance of LTP and lower thresholds for depotentiation – defined as the process of reversing the previous LTP, returning the synapse to its original state – and long-term depression. This shift in the balance of LTP and LTD could impair the encoding of memories and enhance the erasure of memories, therefore contributing to the cognitive deficits experienced by aged individuals.[56]

The hippocampus is one of the most intensely studied regions of the brain, in terms of aging, due to the fact that memory processes that depend on the hippocampus are highly susceptible to disruption with advanced age. The available data suggests that alterations in hippocampal morphology, biochemistry, and physiology are linked to a shift in the susceptibility to induction of synaptic plasticity.[59,60] Since several forms of hippocampal synaptic plasticity are dependent on calcium channel function and subsequent Ca^{2+} dependent processes, including the Ca^{2+} dependent enzymes, there is believed to exist a strong link between altered Ca^{2+} homeostasis and memory deficits associated with aging.[61] One of the main processes by which this is supposed to happen is that the altered Ca^{2+} regulation leads to an increase in the amplitude of the afterhyperpolarization phase - the action potential's phase where the cell's membrane potential falls below the normal resting potential - which shapes the threshold for LTP induction. The synaptic NMDA receptors are also affected, and so the LTP maintenance and expression, representing the reduced cell excitability and the increased susceptibility to LTD a functional lesion in the memory system.[59,62,63]

Although normal aging may be accompanied by some loss of neuronal elements, including changes in the branching of axons and in the number or size of synaptic contacts, the overall results suggest that significant cell loss is not required for the appearance of age-related cognitive deficits.[56,60,64,65]

Therefore, there appears to be an evident conclusion that cognitive deficits and brain aging are not due to a single factor, but to an extremely intricate multifactorial route where several processes simultaneously interact and operate at different levels of functional organization.[59,66]

In fact, the recent research surrounding aging and senescence describes the phenomenon as a network between programmed and damage-related factors: while the programmed theories imply that aging follows a biological timetable, with progressive changes in the genetic maintenance system together with endocrine and immunological factors; the damage theories highlight environmental assaults to the organisms that induce cumulative damage at various levels.[67] As a consequent inference, in complex systems, such as the brain, aging is believed to depend on an interaction among three major variables: time; the constitutional and genetic background of the vehicle within which time flows and its evolution; and the cumulative impact of encounters with diverse events such as stress, hypertension, oxidation, head trauma, exposure to xenobiotics, and so on.[45]

Concluding from that, the assumption that lower memory scores in groups of older people reflect changes that are intrinsic to aging, that is to say, only caused by the passage of time, is a false statement. Such changes also reflect the impact of some specific, probably ordinary, but theoretically preventable events. Aging may not cause these events but may increase the probability of encountering them.

Differentiating the inevitable consequences of time from the cumulative but preventable impact of stochastic phenomena embedded within time is one of the most important goals of current research on aging.[1,45]

Why do certain individuals age successfully?

One of the main questions that are raised is why certain individuals age successfully? It is known that while some elderly subjects show losses, in different degrees of severity in various tests of cognitive performance, even without these deviations being precipitated by illnesses, others are able to perform within the normal range, sometimes even higher when compared with younger adult subjects.

Evidencing the relevance of this fact, several studies show that the individual rates of change in cognitive function through aging express considerable heterogeneity and that this inter-individual variability seems to increase within aging. This is present not only in cognition but in other biological, social, and behavioral variables, which strongly challenges age-based generalizations and clinical prognosis.[68–71]

Bearing this in mind, there may be a group of individuals who, because of either good environmental fortune or genetic makeup, may manage to age without major changes of mental acuity, keeping the memory performance levels distinctly above average normative values. This is the group that is targeted by the Northwestern SuperAging Project.[1,72] In this study, several relevant conclusions were taken:

- MRI imaging revealed that the anterior cingulate cortex – a region involved in certain higher-level functions, being indirectly related to episodic memory – of SuperAgers was significantly thicker than the same area in aged individuals with normal cognitive performance, and, more than that, were also greater than the same area in a group of much younger, middle-aged individuals;
- Unusually low incidence of the ε4 allele of apolipoprotein E (ApoE) – whose presence promotes earlier AD onset[73] – was found in the SuperAgers' group providing a potential substrate for the apparent resistance of the group to age-related decline of cortical functionality, cortical atrophy, and Alzheimer-type degenerative changes;
- Postmortem detection of neurofibrillary tangles – known markers of Alzheimer pathology but also common in elderly individuals with mild or not known cognitive or neurological impairment[74,75] – revealed that their density in the anterior cingulate region was lower in SuperAgers than in the control groups, suggesting that this resistance may promote the preservation of memory function in advanced age. In what concerns the amyloid plaques no relevant difference was found and actually greater density was discovered in elderly individuals identified as cognitively normal, which is consistent with recent reports showing that amyloid plaque density is poorly correlated with cognitive states[75,76];
- There were no differences in total neuronal size or count between subject groups, with this finding being consistent with other studies showing that neuronal number

and size do not necessarily vary with changes in age-related brain structure or cognition[77,78];

- The number of von Economo neurons – a still not well-studied group of neurons that are suggested to have selectively emerged in phylogenetically advanced species playing an important role in the rapid transmission of behaviorally relevant contextual information related to social interactions[79–81], and that are also especially vulnerable in neurodegenerative disorders[82,83] – was considerably higher in the anterior cingulate of SuperAgers compared with age-matched controls and individuals with pre-dementia states.

In conclusion, this study showed that excellent memory capacity in late life is a biological possibility and, more than that, there exists a biological signature which may provide a foundation for future exploration of the factors that promote resistance to age-related involutional phenomena.[72]

Theories on neurocognitive aging

Relevant to this is the definition of the terms brain reserve and cognitive reserve. The reserve concept accounts for the susceptibility differences between individuals to age-related or pathologic brain changes.

Brain reserve is a passive model that can be defined as the brain's resilience, as it can tolerate more damage before it reaches a critical threshold for clinical symptoms to appear.[84] The definition was initially restricted to an increased brain size and the number and dimensions of neuronal connections[85,86], but today it is well-known that this model cannot be entirely quantitative as the growth of new neurons, in the form of neurogenesis, when in stimulating environments, can be highly significant.[87,88] More than that, there is evidence that this static definition makes sense being interdependent and related with the dynamic concept of cognitive reserve, creating the notion of global reserve. Cognitive reserve is a model in that, in the face of neurodegenerative changes that are similar in nature and extent, individuals vary considerably in the severity of cognitive aging and clinical dementia symptoms.[89] It suggests that early and mid-life intelligence and environmental factors such as education, linguistic ability and occupation, as well as lifelong dietary and lifestyle habits, or even cognitively stimulating behaviors, personality

factors and the like, contribute to a reserve that protects against decline despite neuropathology or age-related damage.[84,90,91] This proposition, although receiving both enthusiastic[92] and reluctant[93] support by recent studies, opens an optimistic window showing that the brain, both passively and actively, attempts to cope with brain changes, and that even modifications in lifestyle later in life may have an impact against age-related cognitive decline.

Therefore, this raises an important question about the factors that contribute to this resilience since cognitive reserve may be based on a more efficient utilization of the operating brain networks or on an enhanced ability to recruit alternative brain networks as necessary. Recent studies aim to distinguish or combine the neuroscience models of reserve and compensation.[94]

Compensation is defined as the brain's capacity to maximize performance in the face of impairment by using different structures or networks previously not engaged. Several recent studies indicate that there is an ability to perform the same task using different neural circuitry in older adults, namely by recruiting prefrontal cortex regions contralateral to those most active in younger adults, which also happens in high vs low-performing older adults, having bilateral prefrontal activity and therefore reducing the characteristic hemispheric asymmetry of cognitive processes[95–97]; there is also a posterior-anterior shift where age-related changes in the brain negatively affects occipital, parietal and medial-temporal activity, overactivating the prefrontal region[98,99]; and the characteristic older age's loss of default network activity deactivation is probably compensated by hippocampal and prefrontal overactivation.[100,101]

This compensation model, together with the dedifferentiation hypothesis – an alternative vision which states that there is an age-related decreased processing specificity or regional specialization, being a negative plasticity view in contrast, but possibly harmonizing, with the beneficial compensatory over-recruitment view[102,103] – challenge the traditional doctrine of localization of function, the idea that brain functions were only mediated by and localized in specific brain regions throughout all the individuals life.

Considering all of this, one of the main proposed theories about the neurocognitive aging is the Scaffolding Theory of Aging and Cognition (STAC)[104], which integrates evidence from structural and functional neuroimaging to explain how the combined effects of adverse and compensatory neural processes produce varying levels of cognitive

function. According to STAC, the brain responds to the both previously described structural and functional range of neural challenges by forging alternative neural circuitry, called scaffolds, which are represented by patterns of overactivation and permits individuals to maintain a high level of cognitive function at advanced ages. The extent of the neural deterioration together with the effectiveness of new compensatory scaffolds, allow for the prediction of the overall level of cognitive function. It is also important to state that scaffolding is affected by experiences, like new learning, enhanced cardiovascular and global health, exercise, stimulating activities and cognitive training, as well as life-course events, which is a designation that integrates the influences of important determinants through the course of aging, as the accumulation of life experiences, genetic and environmental impact, that either enhance or deplete brain resources. With this said, scaffolding is a lifelong process, beginning in childhood and moving across the entire lifespan, where the individual is confronted with cognitive challenges to which the brain must adapt.[104–107]

This is still a theory on test, and the relevance of the positive compensating factor to age-related cognitive impairment, in comparison with the negative dedifferentiation influence, is being questioned in recent studies[108,109] based on a probable overvalued interpretation of overactivation of neural circuitry (mainly recognized by cross-sectional analyses) compared to the brain's under-recruitment phenomenon (mostly observed in longitudinal analyses)[110–112]. Taking this into consideration, some studies claim that the brain's maintenance view, which focuses on a relative lack or postponement of senescent anatomical and neurochemical brain changes as the key to conservation of the activation patterns that resemble those of younger adults, is the best interpretation to proficient performance in older adults. This theory states that neurocognitive interventions do not induce novel brain re-adaptations in older adults but may improve performance by reducing age-related changes in various aspects of the brain's physiology. For this reason, maintaining the integrity of the brain could be the crucial determinant for the preservation of memory and cognition in old age.[7,113]

Despite the evident lack of certainty that is the corollary of a theory, it appears to be an important conclusion that the brain and its memory are continuous, dynamic and factor-dependent processes that suffer changes throughout an individual's lifespan that influence

their performance at older ages, therefore opening a way for possible significant preventive interventions that could truly impact age-related memory decline.

Preventive Interventions and their Efficacy

Given the increase in life expectancy and consequently in the number of aged inhabitants, memory and cognitive decline is becoming an important concern not only for the elderly but for the general population. This is reflected by the growing number of patients with a fear of dementia or concerns about their own forgetfulness, being given to these concerns further importance despite the still existent undervaluation in clinical practice.[114,115]

One important definition is the Mild Cognitive Impairment (MCI): this involves a cognitive decline greater than normally expected for an individual's age and education level but which does not notably interfere with activities of the daily life.[116] It is believed to affect 16% to 20% of people over the age of 65 years, according to the majority of the reviewed worldwide studies from a 2013 review.[117] There is an amnestic subtype, where memory loss is the predominant symptom, which is known to be a transitional stage between normal aging and early dementia, frequently seen as a prodromal, but already altered, stage of AD.[118]

Understandably, one of the main concerns of an individual who recognizes some memory decline is the development of AD. This happens because of the devastating effects of this chronic neurodegenerative disease, characterized in the earlier phases by memory loss, but which eventually leads to a near complete loss of cognitive abilities, with a short life expectancy after the diagnosis[119,120]. This is becoming an increasingly common condition in older people, being estimated that there are 5,5 to 10 million new cases per year, globally, with huge costs for the health systems, without any real or effective answers to the issue.[121–123]

The discouragingly small efficacy and, especially, effectiveness – which defines how well a therapy works in practice, rather than in just clinical trials – of the current AD

or MCI treatments, despite the huge investment in research, reinforces the importance of a focus on preventive interventions to act before the development of the condition.[8,10,124,125]

There is some evidence that both AD and age-associated cognitive impairment reflect vulnerability of some of the same neural circuitry[65], with common altered areas, like the hippocampus and the white matter, but while normal aging produces significant changes in the prefrontal cortex, in AD the entorhinal cortex does appear to be significantly impacted early on. It seems that aging increases the vulnerability to the emergence of AD and that these degenerative changes may be responsible, at least in part, for age-related alterations of cognitive function as well.[1]

With this said, the aim of the present review is not to center on the diseases themselves but to give emphasis on the influences of aging in memory, presenting the most studied possible preventive interventions on healthy people, affected by normal aging and that may possibly protect them from MCI, dementia or other important memory impairment conditions.

Pharmacologic Interventions

Regarding the pharmacologic interventions research, age-related physiological memory impairment is not seen, by the scientific community, as a relevant issue and, therefore, a lot of investigation has only been made about the possible pharmacologic answer to AD. However, so far, all efforts to develop therapies targeting specific AD-related pathways have failed or have insignificant effectiveness in clinical practice.

There are still a limited number of approved drugs, and even those are not disease-modifying and have a short-term symptomatic effect, creating a great deal of doubt over the cost-effectiveness of their usage. The ineffectiveness of the agents for memory disorders may result from the concept of targeting pathology rather than the pathophysiology. Disease-modifying therapeutics should therefore aim for brain network repair, especially synaptic repair and regeneration, although that has proven to still be too ambitious in what concerns the theory to practice application of the current knowledge.[126–128]

Cholinesterase inhibitors

Cholinesterase inhibitors, like donepezil, galantamine, and rivastigmine, are approved for use in patients with dementia in an attempt to slow down cognitive and functional decline, where they have a modest but significant symptomatic effect, although with the presence of secondary and adverse discontinuation effects. They work by inhibiting acetylcholinesterase and therefore preventing the decline of the concentration of acetylcholine, a chemical involved in neurotransmission.[129–131] In MCI, cholinesterase inhibitors were not associated with any delay at the onset of AD and the risks associated with their usage are proven to not be negligible.[132,133] In cognitively normal older adults, besides some evidence of semantic encoding aiding[134], there are no studies that attest any effect of these drugs in the prevention of age-related memory decline.

N-methyl-d-aspartate (NMDA) glutamate receptor antagonists

With the main example being memantine, these drugs are thought to selectively block the neurotoxic effects associated with abnormal transmission of glutamate. Despite the lack of consistent evidence for sufficient clinical effects, memantine is approved for use as an add-on to ongoing cholinesterase inhibitor therapy for moderate to severe AD.[135–139] There is no evidence of any positive effects of NMDA receptor antagonists as a preventive memory impairment intervention in MCI or healthy older adults.[140]

Hormonal therapies

Estrogen

Some observational and laboratory-based studies have suggested that postmenopausal hormone treatment may improve cognitive function[141,142], however several studies demonstrate that estrogen alone or estrogen plus progesterone therapies do not improve cognitive functioning but actually have an adverse effect on the health, increasing the risk of clinically meaningful cognitive decline.[143–146] A recent study relaunched the debate around the usage of estrogens stating that estrogen receptors produce both enhancements and impairments in cognition depending on task attributes, memory systems and features of the individual such as age, reproductive status, and general

health.[147] Therefore, further research is needed to determine when and what types of cognitive functions could benefit from estrogen therapies.

Testosterone

Reduction in testosterone levels in men during aging is associated with cognitive decline and risk of dementia.[148] However, there are controversial findings related to the positive effect of testosterone replacement in memory and global cognition. While some studies indicate modest improvements[149–151], others show no consistent relationship.[152–154] Many variables of the complex interaction between testosterone and the brain, like age, sex, current endocrine status, treatment dosing, timing and even the application route seem to considerably affect the outcomes.[155,156] Therefore, more research is required to investigate whether there is a window of time in which this hormonal therapy could be beneficial as a preventive measure.

Dehydroepiandrosterone (DHEA)

The adrenal prohormone dehydroepiandrosterone (DHEA) and its sulphate conjugate (DHEAS) exert many biological activities in different tissues and organs, being believed that its neuro-stimulatory action and its anti-cortisol mechanism of action have a neuroprotective effect. The body concentration of this neurosteroid, the most abundant that is synthesized de novo in the central nervous system, decrease with age by 10% per decade, reaching the lowest point after the age of 80.[157] Laboratory studies show that DHEA supplementation is associated with improved learning and memory in aged mice.[158,159] However, DHEA oral treatment in normal or demented human subjects has produced conflicting and inconsistent results. A study suggested that DHEA administration led to improved episodic memory retrieval in healthy young men[160], while another concluded that the opposition of cortisol effects reduce distraction and may enhance working memory in young women[161], and another found positive regulatory effects on the influence of emotion in memory.[162] However, many other studies suggest that DHEA supplementation has no benefit on cognitive performance in older adults.[157,163–166] Despite this, there seems to exist a positive correlation between some of the multiple effects of the DHEA and the cognition processes as there is still the need for more research to understand the ways in which it can be used as a preventive intervention for age-related memory decline.

Dietary measures

Nutrition is known to play a crucial role in an individual's health. In what concerns the brain's memory systems, it is notorious that under or over nutrition are associated with cognitive decline[167], and that there are some dietary patterns, like the Mediterranean diet – composed by high consumption of vegetables, legumes, fruits, cereals, fish, dairy products, red wine and unsaturated fats like extra virgin olive oil –that have been proven to protect cognitive functioning.[168–170]

Several studies point to an effective role for certain nutrients, such as antioxidants, omega-3 fatty acids or B-complex vitamins, however, data from randomized controlled trials do not show a homogeneous effect. Confounding factors such as sex, age, education, disease stage, smoking, physical activity, presence of other medical conditions, apolipoprotein E genotype, other dietary components, and different methodological issues could explain the divergent results.[171]

Nevertheless, there is an increasing interest in understanding the real role and in effectively applying diet modifications in postponing, slowing and preventing cognitive decline, especially as part of multi-domain interventions that simultaneously target various lifestyle factors.[172,173]

Nutritional modifications have the advantage of being cost-effective, easy to implement, socially acceptable and generally safe interventions that actually may have a positive impact on many of the organism's systems.[174]

In the following information, the recent findings about different specific compounds that have been especially linked to age-related cognitive decline and dementia prevention will be reviewed.

Antioxidants (vitamin E, A, D, C and K, flavonoids, lignans and carotenoids)

Evidence that free radicals may contribute to the pathological processes of cognitive impairment in aging has led to interest in the use of antioxidants as treatment or prevention, which has been a highly investigated topic in the last few years.

Vitamin E is an antioxidant that protects cells from damage associated with oxidative stress caused by free radicals. Wheat germ, sunflower oil, leafy green vegetables

and almonds are among the best food sources of vitamin E. The brain concentrations of α- and γ-tocopherols compounds (with the first being the most biologically active form of vitamin E and the second the most commonly found in the diet) may be associated with AD neuropathology in interrelated, complex ways.[175]

Among patients with AD, 2000 IU/day of vitamin E apparently resulted in slower functional decline and slower progression of the disease, being safe and free of specific side effects in the elderly.[137,176,177] More than that, it was positively associated with performance in domains of verbal memory in healthy adults.[178] However, some other studies indicate that there is no evidence that vitamin E has benefits in MCI progression or that it improves cognitive function in people with AD.[132,179,180]

This inconsistency derives probably from the difficulty in performing precise and uniform human studies and from a still existent discrepancy in the evaluation of α-tocopherol vs γ- or other tocopherols. Recent studies have revealed that while α-tocopherol supplements show negative or neutral effects on cognitive decline, the studies that give emphasis to the dietary tocopherols show benefits.[181,182]

It appears to be almost consensual that vitamin E deficiency results in weakened cognitive performance, by numerous processes, and that an adequate intake supports healthy brain functions.[175] However, the multiple systemic effects, the paradoxical fact that, in high doses, it has pro-oxidant properties, together with the unfavorable and dangerous events reported in supplementation trials[183], shows that there is a need for new and more specific studies about the efficacy of the preventive use of this substance in memory decline.

About other dietary antioxidants, like vitamins A, D, C and K, flavonoids, lignans and carotenoids, there is also reliable evidence of debilitated cognitive function in the case of deficit, and of the positive effects of the presence of these components in high doses in the organism, yet the lack of consistent studies depreciates the predictable preventive efficacy of this supplementation, especially when used in combination.[175,178,179,184–188] As a result, there is indication that dietary intake of antioxidants, instead of supplements, can play a significant role in the prevention and interventional treatment of MCI and AD.

There seems to exist concrete evidence that free radical production does play a critical role in the organism's vascular functioning and so in cognitive impairment conditions, like AD.[189] Therefore, it has become obvious that the resolution of the

combination of these two harmful events (low brain's blood supply and oxidative stress) can have a massive relevance in the treatment and prevention of memory decline, and that this might be one of the most important reasons why nutritional, micronutrient, and antioxidant strategies work better in dementia prevention than several other single-targeted strategies.(190)

Single antioxidants have shown no benefit against cognitive impairment progression, but when multiple antioxidants are used in combination, they protect against vulnerability to other agents and synergistically potentiate their properties, addressing simultaneously several pathophysiological processes that lead to neurodegeneration.(191)

In conclusion, according the current knowledge, it can only be recommended the increase of the dietary intake of multiple antioxidants, however, with further research and individual biochemical characteristics adaptation, it is predicted that an important role for antioxidant supplementation in the prevention of cognitive decline will occur.

Omega-3 fatty acids

Like the antioxidants, omega-3 fatty acids supplementation has attracted huge attention in the last decade for its probable effect in the prevention of memory impairment conditions. Omega-3 cannot be synthesized by humans so it can only be obtained by supplementation or naturally in the consumption of fish, fish oils, seafood and plants.

Omega-3 belongs to a class called polyunsaturated fatty acids (PUFA), which are integral membrane lipids that serve to maintain both the structure and function of neuronal membranes. Its incorporation in the membrane leads to an increased membrane fluidity that can raise the number and affinity of receptors in the synapse and improve neurotransmission. Such fluidity is important in promoting synaptic plasticity which is essential for learning, memory, and other complex cognitive processes. They also have an important role as second messengers that modulate inflammation, oxidative stress, and neuronal health.(192) The main components are docosahexanoic acid (DHA) – the major omega-3 fatty acid in the brain – and eicosapentaenoic acid (EPA). Essential fatty acids deficiency during infancy delays brain development, and in aging accelerate deterioration of brain functions.(193)

Many studies have been made in the last few years about the relationship between omega-3, memory performance and its decline in diverse groups, showing multiple results.

When it comes to patients with proven AD, the results mainly show that clinical trials find no convincing evidence for the efficacy in the treatment of advanced stages of this dementia. However, many of these trials produced intriguing data suggesting that the beneficial effects of omega-3 fatty acid supplementation may depend on the stage of disease, other dietary mediators, and apolipoprotein E status.[192,194–197]

In what concerns healthy adults, though, the results are different. While three studies found that supplementation did not substantially affect cognitive performance[197–199], a much higher number of studies suggested that learning and memory function improved with an high intake of omega-3 fatty acids taken as a supplement but especially with an increased weekly consumption of fatty fish or seafood. More than that, it was found that this measure importantly supports global cognitive health, and so, significantly reduces the risk of age-related memory impairment and incident AD.[200–206]

Supporting this, the trials with MCI patients observed that increased intakes of DHA and EPA improved memory performance and reduced the risk of progression to dementia.[207–210] Some other studies have related that, despite little or no evidence of improvement in moderate or severe AD, there were positive effects in patients with mild or very mild AD, showing that omega-3 fatty acids may be beneficial in disease onset, when there is slight impairment of brain function.[211,212]

From this it can be concluded that there is an important role for omega-3 fatty acids in the prevention of memory decline conditions in early stages of impairment or in healthy adults. This can be reached particularly by an increased dietary intake, since there are still no consensual models of the specificities of its supplementation.

Adding to this, studies suggest that omega-3 may be more effective when used in conjunction with antioxidants.[210,213]

B-group vitamins

B-group vitamins are a group of organic compounds which are essential for the normal physiological functioning of several body processes. Since they are not synthesized endogenously, these vitamins must to be obtained from dietary sources like cereal grains, vegetables, meat, dairy and eggs. In the brain, B-complex vitamins seem to have a particular impact on physiological functioning, related to their general metabolic functions,

effects on genomic and non-genomic methylation, and important roles in neurochemical synthesis.[214]

According to the predominant theory in this area, the homocysteine hypothesis, the role of the B-group vitamins in the age-related cognitive impairment is related to an amino-acid called homocysteine. It states that hyperhomocysteinemia may contribute to the cognitive decline pathophysiology by direct neurotoxic and vascular mechanisms, since homocysteine is a known risk factor for vascular disease.[215,216] Therefore, an increased plasma homocysteine level has revealed to be a strong, independent risk factor for the development of cognitive decline and dementia.[217,218]

Since there is much evidence that the homocysteine serum level can be lowered by high intake of folic acid (vitamin B9), vitamin B12 and B6, the prospect that these vitamins supplementation could lower the risk of dementia has been raised.[219–221] However, although the vitamin supplement regimes are effective in reducing homocysteine levels, there is no consistent and systematic evidence of a significant effect on cognitive function or cognitive aging.[222–224]

Nonetheless, there is also effective evidence that the total B-vitamins intake is associated with better cognitive function in cognitively impaired elderly individuals suffering from AD and MCI.[215,220,221]

The findings on this theme are discrepant and controversial. What is supposed is that, despite sharing metabolic pathways, homocysteine, vitamin B12, B6 and folate are differently related to specific cognitive endings.[225] More than that, it appears that the full range of the eight B-complex vitamins work inter-linked at the cellular level, defining themselves as essential for multiple aspects of brain function.[214] Therefore, treatments containing all of the B-group vitamins should be more effective than small sub-groups of B vitamins, and so multivitamin research needs to be addressed, counterbalancing the tendency of the studies to be only focused on B6, B9 and B12 vitamins.[226]

Also, as happens with other compounds, B-vitamins, as a group and individually, also work intricately in concert with other vitamins, minerals and micronutrients, and so an investment is needed in the potential multi-nutritional intervention of the full-range components of a balanced diet.[227] In order to achieve correct and proven application of B-complex supplementation treatment for the memory decline field, further and broader studies are necessary.

Gingko Biloba

Extracts of the leaves of ginkgo biloba have a long history of being used as a traditional medicine for various health disorders as they are a known regulator of the organism's general physiological status in response to stressors. The mechanisms of action in the brain are thought to be based on the gathering of several components of the extract, like flavonoids, terpene lactones, and ginkgolic acids, and include increasing blood supply by dilating blood vessels and reducing platelet aggregation, improving cerebral glucose utilization, improving neurotransmitter systems and reducing the density of oxygen free radicals.[228,229]

This has been the case of much interest and a base for multiple studies with many different outcomes. Some have shown negative results stating that ginkgo biloba provides no measurable beneficial effects in memory in adults with healthy cognitive function[229–231], and also that there is no evidence that confers benefits in neither individuals with MCI[232,233] nor in mild to moderate dementia.[234]

Nonetheless, more recent studies have found that ginkgo biloba, especially the extract EGb761 in high doses (240mg/day), appears to be more effective than placebo in the treatment of dementia, stabilizing or slowing the decline.[235–237] Other studies revealed that it also has a significant effect at promoting episodic memory function in MCI patients[237,238] and at improving free recall of appointments in middle-aged healthy adults.[239] More than that, a 20-year study reported that cognitive decline in a non-demented elderly population was lower in subjects who consistently used EGb761 extract.[240] In addition, it appears to be safe in use with no excess side effects.

Further study is still needed especially in what concerns the bases of using ginkgo biloba as a preventive intervention, however it reveals to probably be a promising and valuable supplement.

Physical Exercise

Physical exercise has a long-term health-promoting effect, being known for an increase in life expectancy and in the overall quality of life by many different mechanisms.[241] In the brain, evidence supports the role of exercise in modifying

metabolic, structural, and functional dimensions of the brain and in preserving cognitive performance, conveying a protective effect against cognitive decline in aging and AD.[242]

It is also recognized that exercise training promotes extensive vascular changes in both the peripheral and cerebral vasculature, such as improving organ blood flow, inducting antioxidant pathways, and enhancing angiogenesis and endothelial regeneration. Vascular dysfunction is profoundly involved in neurodegenerative processes, therefore, modifying these vascular risk factors could effectively have a decisive role in slowing the trajectory of age-related memory decline.[243] More than that, it is also believed that an important influence in enhancing neurogenesis and improving synaptic plasticity exists, especially in the hippocampus and medial temporal lobe, brain areas that are important for learning and memory.[243,244]

This is proved by many clinical trials involving exercise interventions that demonstrate positive effects on cognitive performance. Despite some other trials that show minimal or no effect[245,246], there is much evidence that exercise is valuable for brain's performance and consequently memory function, which contributes to attenuate cognitive decline and even to delay the onset of dementia in the elderly.[242,247–253]

However, it remains to be established to what extent exercise interventions in old age can improve brain plasticity beyond just the preservation of function. Divergent evidence suggests altered effects from different structuration, intensity and duration of the exercise programs, some assessing the beneficial effects of short-term exercise[254], while others declare the benefit of resistance training.[255] It is suggested that different types of programs should be selectively aimed at different populations according to age, presence and stage of MCI or AD pathology, vascular and metabolic risk factors, physical capacity and genetic variability.[244]

Although further and detailed research is needed, physical exercise interventions targeting brain health improvement through neuroprotective mechanisms, especially when combined with other nutritional, pharmacological and cognitive training interventions[256–258], show promise for preserving cognitive performance and effectively prevent age-related memory decline.

Cognitive Training

As it was observed earlier, studies suggest that mentally active individuals are at a lower risk of cognitive decline and dementia in old age.[259,260] Therefore, taking this into account, there could exist intensive programs of specific cognitive training that may be able to improve the cognitive abilities of the individual and help preventing age-related memory impairments.

Different types of programs with different focuses have been developed and, generally, in healthy individuals, cognitive training resulted in improved performance on levels of memory and cognitive function, with these effects still present years after the intervention, which positively predicts a decrease in the pace of cognitive aging.[261–265] Given the probable assumption that training will not improve functioning in patients with progressive conditions, fewer studies have been carried out in patients with MCI or AD, however, the so called cognitive rehabilitation revealed to be effective at least in delaying the continuous progression of cognitive impairment.[266–268]

At the structural level, cognitive training in healthy adults has been associated with augmented brain volume, cortical thickness and density of white matter tracts, while at the functional level, improved brain metabolism and patterns of increased and decreased task-related brain activation were exhibited.[269]

However, it is not yet clearly established by what mechanisms do training acts on cognitive aging. Furthermore, one of the main difficulties is the recurrent failure of brain training to transfer benefits to untrained abilities, since the benefits are often only related to a specifically targeted skill.[261] Cognitive performance on daily life activities is understandably the main goal of an effective training program, and recent results suggest an improvement in the generalization and transfer of benefits of programs that incorporate perceptual speed and accuracy functions while strongly engaging individually adapted neuromodulatory systems and not neglecting attention and reward.[270–272] Related to that, some studies show advantages in errorless techniques in learning novel associations, contrasting to errorful techniques.[273,274]

Nevertheless, many of the published intervention studies show major limitations in the coherence of design or analysis methods, which challenge the definitive conclusions about the efficacy of training in everyday activities.[275]

Many recent studies also address the synergistic effects of simultaneous cognitive training and physical exercise on cognition in older adults, features that contribute differentially to improving brain health, offering greater potentials on daily life functioning, which usually involves the recruitment of multiple abilities and resources.[276–279] Additionally, the combination of age-specific brain non-invasive stimulation protocols during cognitive training, which may potentially facilitate cognitive and brain plasticity and play a significant role in improving or delaying cognitive decline in old age, has also been studied.[280]

It is becoming an inherent statement that cognitive training could be an active and valuable preventive intervention in age-related cognitive decline. However, its role in combined interventions, inserted in a global active lifestyle, should not be neglected since the cognitive training programs still have a weaker effect when acting just by themselves.[281]

Non-Invasive Brain Stimulation and Deep Brain Stimulation

Non-Invasive Brain Stimulation (NIBS) is a technique which involves altering neural activity by inducing long-term after effects on cortical excitability and neuronal plasticity emulating long-term potentiation and long-term depression.[282] The two most commonly used techniques in humans are repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). This is a safe method, that can be used throughout an entire lifespan[283] and which can have many benefits compared to other types of interventions, like avoiding systemic side-effects.

Some studies have uncovered beneficial effects from NIBS interventions on cognition and brain functions in MCI, by avoiding or reversing cognitive deficits[284–286], and other early trials have also showed that there could be a promising effect of NIBS on the cognitive function in both physiological and pathological aging.[287] However, no definitive conclusions on the efficacy and specificity of NIBS can be advanced at this stage, especially regarding preventive interventions.

In relation to Deep Brain Stimulation (DBS), this involves the intervention over pathological brain states using continuous and direct electrical current, which is applied focally and directly in the neural elements. Early clinical data in some patients with AD

suggests that DBS may be connected with stabilization or improvement in memory and cognitive impairment.[288,289] Despite DBS being reversible, adjustable and titratable, it is still an invasive intervention that carries many potential ethical dilemmas related to a possible use in the prevention of cognitive decline.

In conclusion, despite the need for further and more detailed research on all the addressed interventions, beneficial effects were especially found in the increased intake of ginkgo biloba, antioxidants, omega-3 fatty acids and the full range of B-group vitamins, with the best effects encountered in their combined inclusion in the diet instead of specific supplementation. More than that, physical exercise combined with cognitive training, probably together with non-invasive brain stimulation techniques, have proven to play a significant role as interventions for the prevention of physiological and pathological cognitive and memory decline.

Conclusion

Memory is certainly one of the most complex processes in our brain and organism. Therefore, the current knowledge about the correct mechanisms of its formation and decline is still limited, based only on sometimes consistent or controversial theories. Subsequently, the effect of different factors on the development and vicissitudes of the memory processes is still hardly known.

Furthermore, memory decline has been mainly studied in the context of its pathological behavior, mostly being just addressed the Alzheimer's disease, however, even in this dementia, and despite the hugely expensive research, truly effective treatments have yet to be found. Network based therapies, in contrast with the customary single target based approaches, have shown significant outcomes, revealing successful therapeutic systems that are even able to reverse the cognitive decline of AD.[11,12]

In what concerns physiological age-related memory decline, having common and contrasting features with pathological neurodegeneration, effective treatments have yet to be explored, however, preventive interventions have proven to be increasingly relevant in the cognitive aging.

Beneficial effects have been found in lifestyle changes. Modifications in the diet are believed to play a significant role against cognitive impairment progression, particularly with the inclusion of ginkgo biloba, as well as an high intake of multiple antioxidants (being the most studied vitamin E), together with omega-3 fatty acids and the full range of B-complex vitamins. Physical exercise is also known to have a health-promoting effect by many different mechanisms and, in the brain, is notorious its effect in the prevention of cognitive decline, especially when combined with other interventions. Cognitive training effectively results in long-term improved performance on levels of memory and cognitive function and, in combination with non-invasive brain stimulation techniques, it could be seen as a promising influence as a preventive intervention.

Therefore, it has become gradually more evident that a full lifestyle nutrition and physical activity plan, with adaptations based on the individual's specific impairments, as well as age, sex, biochemical, hormonal and genetic variations, physical and intellectual background and capacity, presence of risk factors, pathologies and other variables; together

with some punctual particular interventions like cognitive training and brain stimulation, represents the present and the future of prevention, and even treatment, in the cognitive decline field.

With that said, further research is required in order to substantiate the true effectiveness of these interventions and to provide detailed strategies of how to correctly apply them as concrete measures in the prevention the age-related memory decline.

References

1. Rogalski EJ, Gefen T, Shi J, Samimi M, Bigio E, Weintraub S, et al. Youthful Memory Capacity in Old Brains: Anatomic and Genetic Clues from the Northwestern SuperAging Project. J Cogn Neurosci. 2013 Jan;25(1):29–36.

2. Baddeley A. Working Memory, Thought, and Action. OUP Oxford; 2007. 356 p.

3. Nilsson L-G, Bäckman L, Erngrund K, Nyberg L, Adolfsson R, Bucht G, et al. The Betula prospective cohort study: Memory, health, and aging. Aging Neuropsychol Cogn. 1997;4(1):1–32.

4. Christensen H, J A, E A, F A, S A, Jacomb P, et al. An analysis of diversity in the cognitive performance of elderly community dwellers: Individual differences in change scores as a function of age. Psychol Aging. 1999;14(3):365–79.

5. Wilson RS, Beckett LA, Barnes LL, Schneider JA, Bach J, Evans DA, et al. Individual differences in rates of change in cognitive abilities of older persons. Psychol Aging. 2002;17(2):179–93.

6. Lindenberger U, Ghisletta P. Cognitive and sensory declines in old age: Gauging the evidence for a common cause. Psychol Aging. 2009;24(1):1–16.

7. Nyberg L, Lövdén M, Riklund K, Lindenberger U, Bäckman L. Memory aging and brain maintenance. Trends Cogn Sci. 2012 May 1;16(5):292–305.

8. Lanctôt KL, Rajaram RD, Herrmann N. Therapy for Alzheimer's Disease: How Effective are Current Treatments? Ther Adv Neurol Disord. 2009 May;2(3):163–80.

9. Yiannopoulou KG, Papageorgiou SG. Current and future treatments for Alzheimer's disease. Ther Adv Neurol Disord. 2013 Jan;6(1):19–33.

10. Bredesen DE, John V. Next generation therapeutics for Alzheimer's disease. EMBO Mol Med. 2013 Jun;5(6):795–8.

11. Bredesen DE. Reversal of cognitive decline: a novel therapeutic program. Aging. 2014 Sep;6(9):707–17.

12. Bredesen DE, Amos EC, Canick J, Ackerley M, Raji C, Fiala M, et al. Reversal of cognitive decline in Alzheimer's disease. Aging. 2016 Jun 12;8(6):1250–8.

13. Atkinson RC, Shiffrin RM. Human Memory: A Proposed System and its Control Processes1. In: Spence KWS and JT, editor. Psychology of Learning and Motivation. Academic Press; 1968 p. 89–195.

14. Budson AE, Price BH. Memory dysfunction in clinical practice. Discov Med. 2005 Apr;5(26):135–41.

15. Glisky EL. Changes in Cognitive Function in Human Aging. In: Riddle DR, editor. Brain Aging: Models, Methods, and Mechanisms. Boca Raton (FL): CRC Press/Taylor & Francis; 2007

16. Cowan N. What are the differences between long-term, short-term, and working memory? Prog Brain Res. 2008;169:323–38.

17. Wager TD, Smith EE. Neuroimaging studies of working memory: a meta-analysis. Cogn Affect Behav Neurosci. 2003 Dec;3(4):255–74.

18. Jaeggi SM, Seewer R, Nirkko AC, Eckstein D, Schroth G, Groner R, et al. Does excessive memory load attenuate activation in the prefrontal cortex? Load-dependent processing in single and dual tasks: functional magnetic resonance imaging study. NeuroImage. 2003 Jun;19(2 Pt 1):210–25.

19. Budson AE, Price BH. Memory Dysfunction in Clinical Practice. Discov Med. 2009 Jul 17;5(25):135–41.

20. Vallar G, Shallice T. Neuropsychological Impairments of Short-Term Memory. Cambridge University Press; 2007. 540 p.

21. Salthouse TA. The processing-speed theory of adult age differences in cognition. Psychol Rev. 1996 Jul;103(3):403–28.

22. Salthouse TA. The aging of working memory. Neuropsychology. 1994;8(4):535–43.

23. Weinert FE, Schneider W. Memory Performance and Competencies: Issues in Growth and Development. Psychology Press; 1995. 466 p.

24. Hasher L, Zacks RT. Working Memory, Comprehension, and Aging: A Review and a New View. In: Bower GH, editor. Psychology of Learning and Motivation. Academic Press; 1988 p. 193–225

25. Hasher L, Zacks RT, May CP. Inhibitory control, circadian arousal, and age. In: hibitory control, circadian arousal, Gopher D, Koriat A, editors. Attention and performance XVII: Cognitive regulation of performance: Interaction of theory and application. Cambridge, MA, US: The MIT Press; 1999. p. 653–75.

26. West RL. An application of prefrontal cortex function theory to cognitive aging. Psychol Bull. 1996 Sep;120(2):272–92.

27. Glisky EL, Rubin SR, Davidson PS. Source memory in older adults: an encoding or retrieval problem? J Exp Psychol Learn Mem Cogn. 2001 Sep;27(5):1131–46.

28. Jennings JM, Jacoby LL. An opposition procedure for detecting age-related deficits in recollection: telling effects of repetition. Psychol Aging. 1997 Jun;12(2):352–61.

29. Nolde SF, Johnson MK, D'Esposito M. Left prefrontal activation during episodic remembering: an event-related fMRI study. Neuroreport. 1998 Oct 26;9(15):3509–14.

30. Davidson PSR, Glisky EL. Neuropsychological correlates of recollection and familiarity in normal aging. Cogn Affect Behav Neurosci. 2002 Jun;2(2):174–86.

31. Craik FIM, Salthouse TA. The Handbook of Aging and Cognition: Third Edition. Psychology Press; 2011. 663 p.

32. Levine B, Svoboda E, Hay JF, Winocur G, Moscovitch M. Aging and autobiographical memory: dissociating episodic from semantic retrieval. Psychol Aging. 2002 Dec;17(4):677–89.

33. Piolino P, Desgranges B, Benali K, Eustache F. Episodic and semantic remote autobiographical memory in ageing. Memory. 2002 Jul 1;10(4):239–57.

34. Heindel WC, Salmon DP, Shults CW, Walicke PA, Butters N. Neuropsychological evidence for multiple implicit memory systems: a comparison of Alzheimer's, Huntington's, and Parkinson's disease patients. J Neurosci Off J Soc Neurosci. 1989 Feb;9(2):582–7.

35. McDaniel MA, Einstein GO. Prospective Memory: An Overview and Synthesis of an Emerging Field. SAGE Publications; 2007. 279 p.

36. West R, Herndon RW, Covell E. Neural correlates of age-related declines in the formation and realization of delayed intentions. Psychol Aging. 2003;18(3):461–73.

37. Kvavilashvili L, Kornbrot DE, Mash V, Cockburn J, Milne A. Differential effects of age on prospective and retrospective memory tasks in young, young-old, and old-old adults. Mem Hove Engl. 2009 Feb;17(2):180–96.

38. Smith RE, Bayen UJ, Martin C. The Cognitive Processes Underlying Event-Based Prospective Memory In School Age Children and Young Adults: A Formal Model-Based Study. Dev Psychol. 2010 Jan;46(1):230–44.

39. Craik FIM. Levels of processing: past, present. and future? Mem Hove Engl. 2002 Nov;10(5–6):305–18.

40. Kuhlmann BG, Touron DR. Older adults' use of metacognitive knowledge in source monitoring: Spared monitoring but impaired control. Psychol Aging. 2011;26(1):143–9.

41. Provyn JP, Sliwinski MJ, Howard MW. Effects of age on contextually mediated associations in paired associate learning. Psychol Aging. 2007;22(4):846–57.

42. Kahana MJ, Howard MW, Zaromb F, Wingfield A. Age dissociates recency and lag recency effects in free recall. J Exp Psychol Learn Mem Cogn. 2002;28(3):530–40.

43. Light LL. Memory and Aging: Four Hypotheses in Search of Data. Annu Rev Psychol. 1991;42(1):333–76.

44. Davidson PSR, Cook SP, Glisky EL. Flashbulb memories for September 11th can be preserved in older adults. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2006 Jun;13(2):196–206.

45. Mesulam M-M. Principles of Behavioral and Cognitive Neurology. Oxford University Press; 2000. 577 p.

46. Bliss TV, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. Nature. 1993 Jan 7;361(6407):31–9.

47. Cooke SF, Bliss TVP. Plasticity in the human central nervous system. Brain J Neurol. 2006 Jul;129(Pt 7):1659–73.

48. Gaiarsa J-L, Caillard O, Ben-Ari Y. Long-term plasticity at GABAergic and glycinergic synapses: mechanisms and functional significance. Trends Neurosci. 2002 Nov;25(11):564–70.

49. Bear MF, Connors BW, Paradiso MA. Neuroscience: Exploring the Brain, 3rd Edition. 3rd edition. Philadelphia, PA: Lippincott Williams and Wilkins; 2006. 928 p.

50. Gerrow K, Triller A. Synaptic stability and plasticity in a floating world. Curr Opin Neurobiol. 2010 Oct;20(5):631–9.

51. Lüscher C, Malenka RC. NMDA Receptor-Dependent Long-Term Potentiation and Long-Term Depression (LTP/LTD). Cold Spring Harb Perspect Biol. 2012 Jun

52. Zhong H, Sia G-M, Sato TR, Gray NW, Mao T, Khuchua Z, et al. Subcellular Dynamics of Type II PKA in Neurons. Neuron. 2009 May 14;62(3):363–74.

53. Lee S-JR, Escobedo-Lozoya Y, Szatmari EM, Yasuda R. Activation of CaMKII in single dendritic spines during long-term potentiation. Nature. 2009 Mar 19;458(7236):299–304.

54. Shoji-Kasai Y, Ageta H, Hasegawa Y, Tsuchida K, Sugino H, Inokuchi K. Activin increases the number of synaptic contacts and the length of dendritic spine necks by modulating spinal actin dynamics. J Cell Sci. 2007 Nov 1;120(Pt 21):3830–7.

55. Purves D. Neuroscience, Fourth Edition. 4th edition. Sunderland, Mass: Sinauer Associates, Inc.; 2008. 857 p.

56. Rosenzweig ES, Barnes CA. Impact of aging on hippocampal function: plasticity, network dynamics, and cognition. Prog Neurobiol. 2003 Feb;69(3):143–79.

57. Kumar A, Foster TC. Neurophysiology of Old Neurons and Synapses. In: Riddle DR, editor. Brain Aging: Models, Methods, and Mechanisms. Boca Raton (FL): CRC Press/Taylor & Francis; 2007

58. Mayford M, Siegelbaum SA, Kandel ER. Synapses and Memory Storage. Cold Spring Harb Perspect Biol. 2012 Jun;4(6).

59. Foster TC. Involvement of hippocampal synaptic plasticity in age-related memory decline. Brain Res Brain Res Rev. 1999 Nov;30(3):236–49.

60. Foster TC. Regulation of synaptic plasticity in memory and memory decline with aging. Prog Brain Res. 2002;138:283–303.

61. Foster TC, Norris CM. Age-associated changes in Ca(2+)-dependent processes: relation to hippocampal synaptic plasticity. Hippocampus. 1997;7(6):602–12.

62. Kumar A, Foster TC. Enhanced long-term potentiation during aging is masked by processes involving intracellular calcium stores. J Neurophysiol. 2004 Jun;91(6):2437–44.

63. Tombaugh GC, Rowe WB, Rose GM. The slow afterhyperpolarization in hippocampal CA1 neurons covaries with spatial learning ability in aged Fisher 344 rats. J Neurosci Off J Soc Neurosci. 2005 Mar 9;25(10):2609–16.

64. Hof PR, Duan H, Page TL, Einstein M, Wicinski B, He Y, et al. Age-related changes in GluR2 and NMDAR1 glutamate receptor subunit protein immunoreactivity in corticocortically projecting neurons in macaque and patas monkeys. Brain Res. 2002 Feb 22;928(1–2):175–86.

65. Hof PR, Morrison JH. The aging brain: morphomolecular senescence of cortical circuits. Trends Neurosci. 2004 Oct;27(10):607–13.

66. Tosato M, Zamboni V, Ferrini A, Cesari M. The aging process and potential interventions to extend life expectancy. Clin Interv Aging. 2007 Sep;2(3):401–12.

67. Jin K. Modern Biological Theories of Aging. Aging Dis. 2010 Aug 1;1(2):72–4.

68. Nelson EA, Dannefer D. Aged heterogeneity: fact or fiction? The fate of diversity in gerontological research. The Gerontologist. 1992 Feb;32(1):17–23.

69. Ylikoski R, Ylikoski A, Keskivaara P, Tilvis R, Sulkava R, Erkinjuntti T. Heterogeneity of cognitive profiles in aging: successful aging, normal aging, and individuals at risk for cognitive decline. Eur J Neurol. 1999 Nov;6(6):645–52.

70. JESTE DV, DEPP CA, VAHIA IV. Successful cognitive and emotional aging. World Psychiatry. 2010 Jun;9(2):78–84.

71. Mungas D, Beckett L, Harvey D, Farias ST, Reed B, Carmichael O, et al. Heterogeneity of Cognitive Trajectories in Diverse Older Person. Psychol Aging. 2010 Sep;25(3):606–19.

72. Gefen T, Peterson M, Papastefan ST, Martersteck A, Whitney K, Rademaker A, et al. Morphometric and histologic substrates of cingulate integrity in elders with exceptional memory capacity. J Neurosci Off J Soc Neurosci. 2015 Jan 28;35(4):1781–91.

73. Liu C-C, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms, and therapy. Nat Rev Neurol. 2013 Feb;9(2):106–18.

74. Price JL, Morris JC. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. Ann Neurol. 1999 Mar;45(3):358–68.

75. Guillozet AL, Weintraub S, Mash DC, Mesulam MM. Neurofibrillary tangles, amyloid, and memory in aging and mild cognitive impairment. Arch Neurol. 2003 May;60(5):729–36.

76. Arriagada PV, Growdon JH, Hedley-Whyte ET, Hyman BT. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. Neurology. 1992 Mar;42(3 Pt 1):631–9.

77. Freeman SH, Kandel R, Cruz L, Rozkalne A, Newell K, Frosch MP, et al. Preservation of neuronal number despite age-related cortical brain atrophy in elderly subjects without Alzheimer disease. J Neuropathol Exp Neurol. 2008 Dec;67(12):1205–12.

78. Peters A. Structural changes that occur during normal aging of primate cerebral hemispheres. Neurosci Biobehav Rev. 2002 Nov;26(7):733–41.

79. Hakeem AY, Sherwood CC, Bonar CJ, Butti C, Hof PR, Allman JM. Von Economo neurons in the elephant brain. Anat Rec Hoboken NJ 2007. 2009 Feb;292(2):242–8.

80. Allman JM, Tetreault NA, Hakeem AY, Manaye KF, Semendeferi K, Erwin JM, et al. The von Economo neurons in frontoinsular and anterior cingulate cortex in great apes and humans. Brain Struct Funct. 2010 Jun;214(5–6):495–517.

81. Butti C, Santos M, Uppal N, Hof PR. Von Economo neurons: clinical and evolutionary perspectives. Cortex J Devoted Study Nerv Syst Behav. 2013 Jan;49(1):312–26.

82. Seeley WW, Carlin DA, Allman JM, Macedo MN, Bush C, Miller BL, et al. Early frontotemporal dementia targets neurons unique to apes and humans. Ann Neurol. 2006 Dec;60(6):660–7.

83. Santillo AF, Nilsson C, Englund E. von Economo neurones are selectively targeted in frontotemporal dementia. Neuropathol Appl Neurobiol. 2013 Aug;39(5):572–9.

84. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. Lancet Neurol. 2012 Nov;11(11):1006–12.

85. 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. Ann Neurol. 1988 Feb;23(2):138–44.

86. Schofield PW, Logroscino G, Andrews HF, Albert S, Stern Y. An association between head circumference and Alzheimer's disease in a population-based study of aging and dementia. Neurology. 1997 Jul;49(1):30–7.

87. van Praag H, Kempermann G, Gage FH. Neural consequences of environmental enrichment. Nat Rev Neurosci. 2000 Dec;1(3):191–8.

88. Brown J, Cooper-Kuhn CM, Kempermann G, Van Praag H, Winkler J, Gage FH, et al. Enriched environment and physical activity stimulate hippocampal but not olfactory bulb neurogenesis. Eur J Neurosci. 2003 May;17(10):2042–6.

89. Whalley LJ, Deary IJ, Appleton CL, Starr JM. Cognitive reserve and the neurobiology of cognitive aging. Ageing Res Rev. 2004 Nov;3(4):369–82.

90. Staff RT, Murray AD, Deary IJ, Whalley LJ. What provides cerebral reserve? Brain J Neurol. 2004 May;127(Pt 5):1191–9.

91. Riley KP, Snowdon DA, Desrosiers MF, Markesbery WR. Early life linguistic ability, late life cognitive function, and neuropathology: findings from the Nun Study. Neurobiol Aging. 2005 Mar;26(3):341–7.

92. Sumowski JF, Rocca MA, Leavitt VM, Dackovic J, Mesaros S, Drulovic J, et al. Brain reserve and cognitive reserve protect against cognitive decline over 4.5 years in MS. Neurology. 2014 May 20;82(20):1776–83.

93. Bennett DA, Arnold SE, Valenzuela MJ, Brayne C, Schneider JA. Cognitive and Social Lifestyle: Links with Neuropathology and Cognition in Late Life. Acta Neuropathol (Berl). 2014 Jan;127(1):137–50.

94. Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. J Int Neuropsychol Soc JINS. 2002 Mar;8(3):448–60.

95. Cabeza R. Hemispheric asymmetry reduction in older adults: the HAROLD model. Psychol Aging. 2002 Mar;17(1):85–100.

96. Cabeza R, Anderson ND, Locantore JK, McIntosh AR. Aging Gracefully: Compensatory Brain Activity in High-Performing Older Adults. NeuroImage. 2002 Nov;17(3):1394–402.

97. Davis SW, Kragel JE, Madden DJ, Cabeza R. The architecture of cross-hemispheric communication in the aging brain: linking behavior to functional and structural connectivity. Cereb Cortex N Y N 1991. 2012 Jan;22(1):232–42.

98. Davis SW, Dennis NA, Daselaar SM, Fleck MS, Cabeza R. Que PASA? The posterior-anterior shift in aging. Cereb Cortex N Y N 1991. 2008 May;18(5):1201–9.

99. Gutchess AH, Welsh RC, Hedden T, Bangert A, Minear M, Liu LL, et al. Aging and the neural correlates of successful picture encoding: frontal activations compensate for decreased medial-temporal activity. J Cogn Neurosci. 2005 Jan;17(1):84–96.

100. Persson J, Lustig C, Nelson JK, Reuter-Lorenz PA. Age differences in deactivation: a link to cognitive control? J Cogn Neurosci. 2007 Jun;19(6):1021–32.

101. Miller SL, Celone K, DePeau K, Diamond E, Dickerson BC, Rentz D, et al. Age-related memory impairment associated with loss of parietal deactivation but preserved hippocampal activation. Proc Natl Acad Sci U S A. 2008 Feb 12;105(6):2181–6.

102. Payer D, Marshuetz C, Sutton B, Hebrank A, Welsh RC, Park DC. Decreased neural specialization in old adults on a working memory task. Neuroreport. 2006 Apr 3;17(5):487–91.

103. Voss MW, Erickson KI, Chaddock L, Prakash RS, Colcombe SJ, Morris KS, et al. Dedifferentiation in the visual cortex: an fMRI investigation of individual differences in older adults. Brain Res. 2008 Dec 9;1244:121–31.

104. Park DC, Reuter-Lorenz P. The adaptive brain: aging and neurocognitive scaffolding. Annu Rev Psychol. 2009;60:173–96.

105. Goh JO, Park DC. Neuroplasticity and cognitive aging: The scaffolding theory of aging and cognition. Restor Neurol Neurosci. 2009;27(5):391–403.

106. Reuter-Lorenz PA, Park DC. Human Neuroscience and the Aging Mind: A New Look at Old Problems. J Gerontol B Psychol Sci Soc Sci. 2010 Jul;65B(4):405–15.

107. Reuter-Lorenz PA, Park DC. How Does it STAC Up? Revisiting the Scaffolding Theory of Aging and Cognition. Neuropsychol Rev. 2014;24(3):355–70.

108. Eyler LT, Sherzai A, Kaup AR, Jeste DV. A review of functional brain imaging correlates of successful cognitive aging. Biol Psychiatry. 2011 Jul 15;70(2):115–22.

109. Jiang X, Petok JR, Howard DV, Howard JH. Individual Differences in Cognitive Function in Older Adults Predicted by Neuronal Selectivity at Corresponding Brain Regions. Front Aging Neurosci. 2017 Apr;9

110. Deary IJ, Whiteman MC, Starr JM, Whalley LJ, Fox HC. The impact of childhood intelligence on later life: following up the Scottish mental surveys of 1932 and 1947. J Pers Soc Psychol. 2004 Jan;86(1):130–47.

111. Nyberg L, Salami A, Andersson M, Eriksson J, Kalpouzos G, Kauppi K, et al. Longitudinal evidence for diminished frontal cortex function in aging. Proc Natl Acad Sci U S A. 2010 Dec 28;107(52):22682–6.

112. Zahodne LB, Glymour MM, Sparks C, Bontempo D, Dixon RA, MacDonald SWS, et al. Education does not slow cognitive decline with aging: 12-year evidence from the victoria longitudinal study. J Int Neuropsychol Soc JINS. 2011 Nov;17(6):1039–46.

113. 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 Jun;41(2):581–95.

114. Coley N, Ousset PJ, Andrieu S, Matheix Fortunet H, Vellas B. Memory complaints to the general practitioner: data from the GuidAge study. J Nutr Health Aging. 2008 Jan;12(1):66S–72S.

115. Pentzek M, Leve V, Leucht V. Subjective memory impairment in general practice : Short overview and design of a mixed methods study. Z Gerontol Geriatr. 2017 May;50(Suppl 2):48–54.

116. Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, et al. Mild cognitive impairment. The Lancet. 2006 Apr 21;367(9518):1262–70.

117. Roberts R, Knopman DS. Classification and Epidemiology of MCI. Clin Geriatr Med. 2013 Nov;29(4).

118. Grundman M, Petersen RC, Ferris SH, Thomas RG, Aisen PS, Bennett DA, et al. Mild cognitive impairment can be distinguished from Alzheimer disease and normal aging for clinical trials. Arch Neurol. 2004 Jan;61(1):59–66.

119. Larson EB, Shadlen M-F, Wang L, McCormick WC, Bowen JD, Teri L, et al. Survival after initial diagnosis of Alzheimer disease. Ann Intern Med. 2004 Apr 6;140(7):501–9.

120. Burns A, Iliffe S. Alzheimer's disease. BMJ. 2009 Feb 5;338:b158.

121. Meek PD, McKeithan K, Schumock GT. Economic considerations in Alzheimer's disease. Pharmacotherapy. 1998 Apr;18(2 Pt 2):68-73; discussion 79-82.

122. Bonin-Guillaume S, Zekry D, Giacobini E, Gold G, Michel J-P. [The economical impact of dementia]. Presse Medicale Paris Fr 1983. 2005 Jan 15;34(1):35–41.

123. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Lond Engl. 2016 Oct 8;388(10053):1545–602.

124. Herrmann N, Lanctôt KL. Pharmacologic management of neuropsychiatric symptoms of Alzheimer disease. Can J Psychiatry Rev Can Psychiatr. 2007 Oct;52(10):630–46.

125. Casey DA, Antimisiaris D, O'Brien J. Drugs for Alzheimer's Disease: Are They Effective? Pharm Ther. 2010 Apr;35(4):208–11.

126. Huang Y, Mucke L. Alzheimer mechanisms and therapeutic strategies. Cell. 2012 Mar 16;148(6):1204–22.

127. Ghezzi L, Scarpini E, Galimberti D. Disease-modifying drugs in Alzheimer's disease. Drug Des Devel Ther. 2013 Dec 6;7:1471–8.

128. Sun M-K, Nelson TJ, Alkon DL. Towards universal therapeutics for memory disorders. Trends Pharmacol Sci. 2015 Jun 1;36(6):384–94.

129. Lanctôt KL, Herrmann N, Yau KK, Khan LR, Liu BA, LouLou MM, et al. Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: a meta-analysis. CMAJ Can Med Assoc J J Assoc Medicale Can. 2003 Sep 16;169(6):557–64.

130. Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD005593.

131. Hogan DB. Long-Term Efficacy and Toxicity of Cholinesterase Inhibitors in the Treatment of Alzheimer Disease. Can J Psychiatry Rev Can Psychiatr. 2014 Dec;59(12):618–23.

132. Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med. 2005 Jun 9;352(23):2379–88.

133. Raschetti R, Albanese E, Vanacore N, Maggini M. Cholinesterase Inhibitors in Mild Cognitive Impairment: A Systematic Review of Randomised Trials. PLoS Med. 2007 Nov;4(11).

134. FitzGerald DB, Crucian GP, Mielke JB, Shenal BV, Burks D, Womack KB, et al. Effects of donepezil on verbal memory after semantic processing in healthy older adults. Cogn Behav Neurol Off J Soc Behav Cogn Neurol. 2008 Jun;21(2):57–64.

135. Schneider LS, Dagerman KS, Higgins JPT, McShane R. Lack of evidence for the efficacy of memantine in mild Alzheimer disease. Arch Neurol. 2011 Aug;68(8):991–8.

136. Rive B, Gauthier S, Costello S, Marre C, François C. Synthesis and Comparison of the Meta-Analyses Evaluating the Efficacy of Memantine in Moderate to Severe Stages of Alzheimer's Disease. CNS Drugs. 2013 Jul;27(7):573–82.

137. Dysken MW, Sano M, Asthana S, Vertrees JE, Pallaki M, Llorente M, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial. JAMA. 2014 Jan 1;311(1):33–44.

138. Ehret MJ, Chamberlin KW. Current Practices in the Treatment of Alzheimer Disease: Where is the Evidence After the Phase III Trials? Clin Ther. 2015 Aug;37(8):1604–16.

139. Matsunaga S, Kishi T, Iwata N. Memantine monotherapy for Alzheimer's disease: a systematic review and meta-analysis. PloS One. 2015;10(4):e0123289.

140. Ferris S, Schneider L, Farmer M, Kay G, Crook T. A double-blind, placebo-controlled trial of memantine in age-associated memory impairment (memantine in AAMI). Int J Geriatr Psychiatry. 2007 May;22(5):448–55.

141. Hideo H, Yoshio O, Kazuo N, Mamoru U, Jo K, Jinsuke Y, et al. In vivo effects by estrone sulfate on the central nervous system-senile dementia (alzheimer's type). J Steroid Biochem. 1989 Jan 1;34(1):521–5.

142. Wolf OT, Kudielka BM, Hellhammer DH, Törber S, McEwen BS, Kirschbaum C. Two weeks of transdermal estradiol treatment in postmenopausal elderly women and its effect on memory and mood: verbal memory changes are associated with the treatment induced estradiol levels. Psychoneuroendocrinology. 1999 Oct;24(7):727–41.

143. Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA. 2003 May 28;289(20):2651–62.

144. Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA. 2004 Jun 23;291(24):2947–58.

145. Almeida OP, Lautenschlager NT, Vasikaran S, Leedman P, Gelavis A, Flicker L. A 20-week randomized controlled trial of estradiol replacement therapy for women aged 70 years and older: Effect on mood, cognition and quality of life. Neurobiol Aging. 2006 Jan;27(1):141–9.

146. Henderson VW. Aging, Estrogens, and Episodic Memory in Women. Cogn Behav Neurol Off J Soc Behav Cogn Neurol. 2009 Dec;22(4):205–14.

147. Korol DL, Pisani SL. Estrogens and Cognition: Friends or Foes? Horm Behav. 2015 Aug;74:105–15.

148. Moffat SD, Zonderman AB, Metter EJ, Kawas C, Blackman MR, Harman SM, et al. Free testosterone and risk for Alzheimer disease in older men. Neurology. 2004 Jan 27;62(2):188–93.

149. Cherrier MM, Asthana S, Plymate S, Baker L, Matsumoto AM, Peskind E, et al. Testosterone supplementation improves spatial and verbal memory in healthy older men. Neurology. 2001 Jul 10;57(1):80–8.

150. Cherrier MM, Matsumoto AM, Amory JK, Ahmed S, Bremner W, Peskind ER, et al. The role of aromatization in testosterone supplementation: effects on cognition in older men. Neurology. 2005 Jan 25;64(2):290–6.

151. Wahjoepramono EJ, Asih PR, Aniwiyanti V, Taddei K, Dhaliwal SS, Fuller SJ, et al. The Effects of Testosterone Supplementation on Cognitive Functioning in Older Men. CNS Neurol Disord Drug Targets. 2016 Apr;15(3):337–43.

152. Maki PM, Ernst M, London ED, Mordecai KL, Perschler P, Durso SC, et al. Intramuscular testosterone treatment in elderly men: evidence of memory decline and altered brain function. J Clin Endocrinol Metab. 2007 Nov;92(11):4107–14.

153. Vaughan C, Goldstein FC, Tenover JL. Exogenous testosterone alone or with finasteride does not improve measurements of cognition in healthy older men with low serum testosterone. J Androl. 2007 Dec;28(6):875–82.

154. Zhao JV, Lam TH, Jiang C, Cherny SS, Liu B, Cheng KK, et al. A Mendelian randomization study of testosterone and cognition in men. Sci Rep. 2016 Feb;6

155. Cherrier MM, Matsumoto AM, Amory JK, Johnson M, Craft S, Peskind ER, et al. Characterization of verbal and spatial memory changes from moderate to supraphysiological increases in serum testosterone in healthy older men. Psychoneuroendocrinology. 2007 Jan;32(1):72–9.

156. Celec P, Ostatníková D, Hodosy J. On the effects of testosterone on brain behavioral functions. Front Neurosci [Internet]. 2015 Feb;9.

157. Maggio M, De Vita F, Fisichella A, Colizzi E, Provenzano S, Lauretani F, et al. DHEA and cognitive function in the elderly. J Steroid Biochem Mol Biol. 2015 Jan;145:281–92.

158. Hoffman SW, Virmani S, Simkins RM, Stein DG. The delayed administration of dehydroepiandrosterone sulfate improves recovery of function after traumatic brain injury in rats. J Neurotrauma. 2003 Sep;20(9):859–70.

159. Bazin M-A, El Kihel L, Boulouard M, Bouët V, Rault S. The effects of DHEA, 3beta-hydroxy-5alpha-androstane-6,17-dione, and 7-amino-DHEA analogues on short term and long term memory in the mouse. Steroids. 2009 Nov;74(12):931–7.

160. Alhaj HA, Massey AE, McAllister-Williams RH. Effects of DHEA administration on episodic memory, cortisol and mood in healthy young men: a double-blind, placebo-controlled study. Psychopharmacology (Berl). 2006 Nov;188(4):541–51.

161. do Vale S, Selinger L, Martins JM, Gomes AC, Bicho M, do Carmo I, et al. The relationship between dehydroepiandrosterone (DHEA), working memory and distraction--a behavioral and electrophysiological approach. PloS One. 2014;9(8):e104869.

162. Sripada RK, Marx CE, King AP, Rajaram N, Garfinkel SN, Abelson JL, et al. DHEA enhances emotion regulation neurocircuits and modulates memory for emotional stimuli. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol. 2013 Aug;38(9):1798–807.

163. Wolf OT, Neumann O, Hellhammer DH, Geiben AC, Strasburger CJ, Dressendörfer RA, et al. Effects of a two-week physiological dehydroepiandrosterone substitution on cognitive performance and well-being in healthy elderly women and men. J Clin Endocrinol Metab. 1997 Jul;82(7):2363–7.

164. van Niekerk JK, Huppert FA, Herbert J. Salivary cortisol and DHEA: association with measures of cognition and well-being in normal older men, and effects of three months of DHEA supplementation. Psychoneuroendocrinology. 2001 Aug;26(6):591–612.

165. Huppert FA, Van Niekerk JK. WITHDRAWN: Dehydroepiandrosterone (DHEA) supplementation for cognitive function. Cochrane Database Syst Rev. 2007 Jul 18;(2):CD000304.

166. Kritz-Silverstein D, von Mühlen D, Laughlin GA, Bettencourt R. Effects of Dehydroepiandrosterone Supplementation on Cognitive Function and Quality of Life: The DHEA and Well-Ness (DAWN) Trial. J Am Geriatr Soc. 2008 Jul;56(7):1292–8.

167. Morley JE. Cognition and nutrition. Curr Opin Clin Nutr Metab Care. 2014 Jan;17(1):1–4.

168. Roberts RO, Geda YE, Cerhan JR, Knopman DS, Cha RH, Christianson TJH, et al. Vegetables, unsaturated fats, moderate alcohol intake, and mild cognitive impairment. Dement Geriatr Cogn Disord. 2010;29(5):413–23.

169. Martínez-Lapiscina EH, Clavero P, Toledo E, Estruch R, Salas-Salvadó J, San Julián B, et al. Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial. J Neurol Neurosurg Psychiatry. 2013 Dec;84(12):1318–25.

170. Valls-Pedret C, Sala-Vila A, Serra-Mir M, Corella D, de la Torre R, Martínez-González MÁ, et al. Mediterranean Diet and Age-Related Cognitive Decline: A Randomized Clinical Trial. JAMA Intern Med. 2015 Jul;175(7):1094–103.

171. Otaegui-Arrazola A, Amiano P, Elbusto A, Urdaneta E, Martínez-Lage P. Diet, cognition, and Alzheimer's disease: food for thought. Eur J Nutr. 2014 Feb;53(1):1–23.

172. Athanasopoulos D, Karagiannis G, Tsolaki M. Recent Findings in Alzheimer Disease and Nutrition Focusing on Epigenetics. Adv Nutr Bethesda Md. 2016 Sep;7(5):917–27.

173. Canevelli M, Lucchini F, Quarata F, Bruno G, Cesari M. Nutrition and Dementia: Evidence for Preventive Approaches? Nutrients. 2016 Mar 4;8(3):144.

174. Swaminathan A, Jicha GA. Nutrition and prevention of Alzheimer's dementia. Front Aging Neurosci [Internet]. 2014 Oct;6.

175. Grimm MOW, Mett J, Hartmann T. The Impact of Vitamin E and Other Fat-Soluble Vitamins on Alzheimer´s Disease. Int J Mol Sci. 2016 Oct;17(11)

176. Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, Grundman M, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. N Engl J Med. 1997 Apr 24;336(17):1216–22.

177. Grundman M. Vitamin E and Alzheimer disease: the basis for additional clinical trials. Am J Clin Nutr. 2000 Feb;71(2):630S–636S.

178. Beydoun MA, Fanelli Kuczmarski M, Kitner-Triolo MH, Beydoun HA, Kaufman JS, Mason MA, et al. Dietary antioxidant intake and its association with cognitive function in an ethnically diverse sample of US adults. Psychosom Med. 2015 Jan;77(1):68–82.

179. Devore EE, Kang JH, Stampfer MJ, Grodstein F. The Association of Antioxidants and Cognition in the Nurses' Health Study. Am J Epidemiol. 2013 Jan 1;177(1):33–41.

180. Farina N, Llewellyn D, Isaac MGEKN, Tabet N. Vitamin E for Alzheimer's dementia and mild cognitive impairment. Cochrane Database Syst Rev. 2017 27;1:CD002854.

181. Morris MC, Evans DA, Tangney CC, Bienias JL, Wilson RS, Aggarwal NT, et al. Relation of the tocopherol forms to incident Alzheimer disease and to cognitive change. Am J Clin Nutr. 2005 Feb;81(2):508–14.

182. Morris MC, Schneider JA, Li H, Tangney CC, Nag S, Bennett DA, et al. Brain Tocopherols Related to Alzheimer Disease Neuropathology in Humans. Alzheimers Dement J Alzheimers Assoc. 2015 Jan;11(1):32–9.

183. Miller ER, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med. 2005 Jan 4;142(1):37–46.

184. Zandi PP, Anthony JC, Khachaturian AS, Stone SV, Gustafson D, Tschanz JT, et al. Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County Study. Arch Neurol. 2004 Jan;61(1):82–8.

185. Li F-J, Shen L, Ji H-F. Dietary intakes of vitamin E, vitamin C, and β-carotene and risk of Alzheimer's disease: a meta-analysis. J Alzheimers Dis JAD. 2012;31(2):253–8.

186. Mecocci P, Polidori MC. Antioxidant clinical trials in mild cognitive impairment and Alzheimer's disease. Biochim Biophys Acta. 2012 May;1822(5):631–8.

187. Nooyens ACJ, Milder IEJ, van Gelder BM, Bueno-de-Mesquita HB, van Boxtel MPJ, Verschuren WMM. Diet and cognitive decline at middle age: the role of antioxidants. Br J Nutr. 2015 May 14;113(9):1410–7.

188. Soutif-Veillon A, Ferland G, Rolland Y, Presse N, Boucher K, Féart C, et al. Increased dietary vitamin K intake is associated with less severe subjective memory complaint among older adults. Maturitas. 2016 Nov;93:131–6.

189. Polidori MC, Pientka L. Bridging the pathophysiology of Alzheimer's disease with vascular pathology: the feed-back, the feed-forward, and oxidative stress. J Alzheimers Dis JAD. 2012;28(1):1–9.

190. Polidori MC, Nelles G. Antioxidant clinical trials in mild cognitive impairment and Alzheimer's disease - challenges and perspectives. Curr Pharm Des. 2014;20(18):3083–92.

191. Yasuno F, Tanimukai S, Sasaki M, Ikejima C, Yamashita F, Kodama C, et al. Combination of antioxidant supplements improved cognitive function in the elderly. J Alzheimers Dis JAD. 2012;32(4):895–903.

192. Jicha GA, Markesbery WR. Omega-3 fatty acids: potential role in the management of early Alzheimer's disease. Clin Interv Aging. 2010;5:45–61.

193. Yehuda S, Rabinovitz S, Mostofsky DI. Essential fatty acids and the brain: from infancy to aging. Neurobiol Aging. 2005 Dec;26 Suppl 1:98–102.

194. Quinn JF, Raman R, Thomas RG, Yurko-Mauro K, Nelson EB, Van Dyck C, et al. Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial. JAMA. 2010 Nov 3;304(17):1903–11.

195. Cederholm T, Palmblad J. Are omega-3 fatty acids options for prevention and treatment of cognitive decline and dementia? Curr Opin Clin Nutr Metab Care. 2010 Mar;13(2):150–5.

196. Burckhardt M, Herke M, Wustmann T, Watzke S, Langer G, Fink A. Omega-3 fatty acids for the treatment of dementia. Cochrane Database Syst Rev. 2016 Apr 11;4:CD009002.

197. Mazereeuw G, Lanctôt KL, Chau SA, Swardfager W, Herrmann N. Effects of ω-3 fatty acids on cognitive performance: a meta-analysis. Neurobiol Aging. 2012 Jul;33(7):1482.e17-29.

198. van de Rest O, Geleijnse JM, Kok FJ, van Staveren WA, Dullemeijer C, Olderikkert MGM, et al. Effect of fish oil on cognitive performance in older subjects: a randomized, controlled trial. Neurology. 2008 Aug 5;71(6):430–8.

199. Forbes SC, Holroyd-Leduc JM, Poulin MJ, Hogan DB. Effect of Nutrients, Dietary Supplements and Vitamins on Cognition: a Systematic Review and Meta-Analysis of Randomized Controlled Trials. Can Geriatr J CGJ. 2015 Dec;18(4):231–45.

200. Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Wilson RS, et al. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. Arch Neurol. 2003 Jul;60(7):940–6.

201. Nurk E, Drevon CA, Refsum H, Solvoll K, Vollset SE, Nygård O, et al. Cognitive performance among the elderly and dietary fish intake: the Hordaland Health Study. Am J Clin Nutr. 2007 Nov;86(5):1470–8.

202. van Gelder BM, Tijhuis M, Kalmijn S, Kromhout D. Fish consumption, n-3 fatty acids, and subsequent 5-y cognitive decline in elderly men: the Zutphen Elderly Study. Am J Clin Nutr. 2007 Apr;85(4):1142–7.

203. Yurko-Mauro K, McCarthy D, Rom D, Nelson EB, Ryan AS, Blackwell A, et al. Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. Alzheimers Dement J Alzheimers Assoc. 2010 Nov;6(6):456–64.

204. Stonehouse W, Conlon CA, Podd J, Hill SR, Minihane AM, Haskell C, et al. DHA supplementation improved both memory and reaction time in healthy young adults: a randomized controlled trial. Am J Clin Nutr. 2013 May;97(5):1134–43.

205. van de Rest O, Wang Y, Barnes LL, Tangney C, Bennett DA, Morris MC. APOE ε4 and the associations of seafood and long-chain omega-3 fatty acids with cognitive decline. Neurology. 2016 May 31;86(22):2063–70.

206. Zhang X-W, Hou W-S, Li M, Tang Z-Y. Omega-3 fatty acids and risk of cognitive decline in the elderly: a meta-analysis of randomized controlled trials. Aging Clin Exp Res. 2016 Feb;28(1):165–6.

207. Sinn N, Milte CM, Street SJ, Buckley JD, Coates AM, Petkov J, et al. Effects of n-3 fatty acids, EPA v. DHA, on depressive symptoms, quality of life, memory and executive function in older adults with mild cognitive impairment: a 6-month randomised controlled trial. Br J Nutr. 2012 Jun;107(11):1682–93.

208. Vakhapova V, Cohen T, Richter Y, Herzog Y, Kam Y, Korczyn AD. Phosphatidylserine containing omega-3 Fatty acids may improve memory abilities in nondemented elderly individuals with memory complaints: results from an open-label extension study. Dement Geriatr Cogn Disord. 2014;38(1–2):39–45.

209. Yurko-Mauro K, Alexander DD, Van Elswyk ME. Docosahexaenoic acid and adult memory: a systematic review and meta-analysis. PloS One. 2015;10(3):e0120391.

210. Jernerén F, Elshorbagy AK, Oulhaj A, Smith SM, Refsum H, Smith AD. Brain atrophy in cognitively impaired elderly: the importance of long-chain ω-3 fatty acids and B vitamin status in a randomized controlled trial. Am J Clin Nutr. 2015 Jul;102(1):215–21.

211. Freund-Levi Y, Eriksdotter-Jönhagen M, Cederholm T, Basun H, Faxén-Irving G, Garlind A, et al. Omega-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer disease: OmegAD study: a randomized double-blind trial. Arch Neurol. 2006 Oct;63(10):1402–8.

212. Canhada S, Castro K, Perry IS, Luft VC. Omega-3 fatty acids' supplementation in Alzheimer's disease: A systematic review. Nutr Neurosci. 2017 May 3;1–10.

213. Cole GM, Ma Q-L, Frautschy SA. Omega-3 fatty acids and dementia. Prostaglandins Leukot Essent Fatty Acids. 2009 Sep;81(2–3):213–21.

214. Kennedy DO. B Vitamins and the Brain: Mechanisms, Dose and Efficacy—A Review. Nutrients. 2016 Jan 28;8(2)

215. Clarke R, Smith AD, Jobst KA, Refsum H, Sutton L, Ueland PM. Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. Arch Neurol. 1998 Nov;55(11):1449–55.

216. Smulders YM, Blom HJ. The homocysteine controversy. J Inherit Metab Dis. 2011 Feb;34(1):93–9.

217. Seshadri S, Beiser A, Selhub J, Jacques PF, Rosenberg IH, D'Agostino RB, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med. 2002 Feb 14;346(7):476–83.

218. Nie T, Lu T, Xie L, Huang P, Lu Y, Jiang M. Hyperhomocysteinemia and risk of cognitive decline: a meta-analysis of prospective cohort studies. Eur Neurol. 2014;72(3–4):241–8.

219. Clarke R. B-vitamins and prevention of dementia. Proc Nutr Soc. 2008 Feb;67(1):75–81.

220. Luchsinger JA, Tang M-X, Miller J, Green R, Mayeux R. Higher Folate Intake is Related to Lower Risk of Alzheimer's Disease in the Elderly. J Nutr Health Aging. 2008 Nov;12(9):648–50.

221. Kim H, Kim G, Jang W, Kim SY, Chang N. Association between intake of B vitamins and cognitive function in elderly Koreans with cognitive impairment. Nutr J. 2014 Dec;13.

222. Aisen PS, Schneider LS, Sano M, Diaz-Arrastia R, van Dyck CH, Weiner MF, et al. High Dose B Vitamin Supplementation and Cognitive Decline in Alzheimer's Disease: A Randomized Controlled Trial. JAMA J Am Med Assoc. 2008 Oct 15;300(15):1774–83.

223. Dangour AD, Whitehouse PJ, Rafferty K, Mitchell SA, Smith L, Hawkesworth S, et al. B-vitamins and fatty acids in the prevention and treatment of Alzheimer's disease and dementia: a systematic review. J Alzheimers Dis JAD. 2010;22(1):205–24.

224. Clarke R, Bennett D, Parish S, Lewington S, Skeaff M, Eussen SJ, et al. Effects of homocysteine lowering with B vitamins on cognitive aging: meta-analysis of 11 trials with cognitive data on 22,000 individuals12345. Am J Clin Nutr. 2014 Aug;100(2):657–66.

225. Morris MS. The Role of B Vitamins in Preventing and Treating Cognitive Impairment and Decline123. Adv Nutr. 2012 Nov 6;3(6):801–12.

226. Haskell CF, Robertson B, Jones E, Forster J, Jones R, Wilde A, et al. Effects of a multi-vitamin/mineral supplement on cognitive function and fatigue during extended multi-tasking. Hum Psychopharmacol. 2010 Aug;25(6):448–61.

227. Kamphuis PJGH, Scheltens P. Can nutrients prevent or delay onset of Alzheimer's disease? J Alzheimers Dis JAD. 2010;20(3):765–75.

228. Smith JV, Luo Y. Studies on molecular mechanisms of Ginkgo biloba extract. Appl Microbiol Biotechnol. 2004 May;64(4):465–72.

229. Birks J, Grimley Evans J. Ginkgo biloba for cognitive impairment and dementia. Cochrane Database Syst Rev. 2007 Apr 18;(2):CD003120.

230. Moulton PL, Boyko LN, Fitzpatrick JL, Petros TV. The effect of Ginkgo biloba on memory in healthy male volunteers. Physiol Behav. 2001 Jul;73(4):659–65.

231. Solomon PR, Adams F, Silver A, Zimmer J, DeVeaux R. Ginkgo for memory enhancement: a randomized controlled trial. JAMA. 2002 Aug 21;288(7):835–40.

232. DeKosky ST, Williamson JD, Fitzpatrick AL, Kronmal RA, Ives DG, Saxton JA, et al. Ginkgo biloba for prevention of dementia: a randomized controlled trial. JAMA. 2008 Nov 19;300(19):2253–62.

233. Snitz BE, O'Meara ES, Carlson MC, Arnold AM, Ives DG, Rapp SR, et al. Ginkgo biloba for preventing cognitive decline in older adults: a randomized trial. JAMA. 2009 Dec 23;302(24):2663–70.

234. McCarney R, Fisher P, Iliffe S, van Haselen R, Griffin M, van der Meulen J, et al. Ginkgo biloba for mild to moderate dementia in a community setting: a pragmatic, randomised, parallel-group, double-blind, placebo-controlled trial. Int J Geriatr Psychiatry. 2008 Dec;23(12):1222–30.

235. Hashiguchi M, Ohta Y, Shimizu M, Maruyama J, Mochizuki M. Meta-analysis of the efficacy and safety of Ginkgo biloba extract for the treatment of dementia. J Pharm Health Care Sci. 2015;1:14.

236. Tan M-S, Yu J-T, Tan C-C, Wang H-F, Meng X-F, Wang C, et al. Efficacy and adverse effects of ginkgo biloba for cognitive impairment and dementia: a systematic review and meta-analysis. J Alzheimers Dis JAD. 2015;43(2):589–603.

237. Zhang H-F, Huang L-B, Zhong Y-B, Zhou Q-H, Wang H-L, Zheng G-Q, et al. An Overview of Systematic Reviews of Ginkgo biloba Extracts for Mild Cognitive Impairment and Dementia. Front Aging Neurosci. 2016 Dec 6;8.

238. Zhao M, Dong Z, Yu Z, Xiao S, Li Y. Effects of Ginkgo biloba extract in improving episodic memory of patients with mild cognitive impairment: a randomized controlled trial. Zhong Xi Yi Jie He Xue Bao. 2012 Jun;10(6):628–34.

239. Kaschel R. Specific memory effects of Ginkgo biloba extract EGb 761 in middle-aged healthy volunteers. Phytomedicine Int J Phytother Phytopharm. 2011 Nov 15;18(14):1202–7.

240. Amieva H, Meillon C, Helmer C, Barberger-Gateau P, Dartigues JF. Ginkgo biloba extract and long-term cognitive decline: a 20-year follow-up population-based study. PloS One. 2013;8(1):e52755.

241. Gremeaux V, Gayda M, Lepers R, Sosner P, Juneau M, Nigam A. Exercise and longevity. Maturitas. 2012 Dec;73(4):312–7.

242. Kirk-Sanchez NJ, McGough EL. Physical exercise and cognitive performance in the elderly: current perspectives. Clin Interv Aging. 2014;9:51–62.

243. Lange-Asschenfeldt C, Kojda G. Alzheimer's disease, cerebrovascular dysfunction and the benefits of exercise: from vessels to neurons. Exp Gerontol. 2008 Jun;43(6):499–504.

244. Duzel E, van Praag H, Sendtner M. Can physical exercise in old age improve memory and hippocampal function? Brain J Neurol. 2016 Mar;139(Pt 3):662–73.

245. Geda YE, Roberts RO, Knopman DS, Christianson TJH, Pankratz VS, Ivnik RJ, et al. Physical exercise, aging, and mild cognitive impairment: a population-based study. Arch Neurol. 2010 Jan;67(1):80–6.

246. Young J, Angevaren M, Rusted J, Tabet N. Aerobic exercise to improve cognitive function in older people without known cognitive impairment. Cochrane Database Syst Rev. 2015 Apr 22;(4):CD005381.

247. Larson EB, Wang L, Bowen JD, McCormick WC, Teri L, Crane P, et al. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann Intern Med. 2006 Jan 17;144(2):73–81.

248. Brown AK, Liu-Ambrose T, Tate R, Lord SR. The effect of group-based exercise on cognitive performance and mood in seniors residing in intermediate care and self-care retirement facilities: a randomised controlled trial. Br J Sports Med. 2009 Aug;43(8):608–14.

249. Erickson KI, Prakash RS, Voss MW, Chaddock L, Hu L, Morris KS, et al. Aerobic fitness is associated with hippocampal volume in elderly humans. Hippocampus. 2009 Oct;19(10):1030–9.

250. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci U S A. 2011 Feb 15;108(7):3017–22.

251. Ahlskog JE, Geda YE, Graff-Radford NR, Petersen RC. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. Mayo Clin Proc. 2011 Sep;86(9):876–84.

252. Hogan CL, Mata J, Carstensen LL. Exercise holds immediate benefits for affect and cognition in younger and older adults. Psychol Aging. 2013 Jun;28(2):587–94.

253. Nishiguchi S, Yamada M, Tanigawa T, Sekiyama K, Kawagoe T, Suzuki M, et al. A 12-Week Physical and Cognitive Exercise Program Can Improve Cognitive Function and Neural Efficiency in Community-Dwelling Older Adults: A Randomized Controlled Trial. J Am Geriatr Soc. 2015 Jul;63(7):1355–63.

254. Nouchi R, Taki Y, Takeuchi H, Hashizume H, Nozawa T, Sekiguchi A, et al. Beneficial effects of short-term combination exercise training on diverse cognitive functions in healthy older people: study protocol for a randomized controlled trial. Trials. 2012 Oct 29;13:200.

255. Cassilhas RC, Viana VAR, Grassmann V, Santos RT, Santos RF, Tufik S, et al. The impact of resistance exercise on the cognitive function of the elderly. Med Sci Sports Exerc. 2007 Aug;39(8):1401–7.

256. Andrade C, Radhakrishnan R. The prevention and treatment of cognitive decline and dementia: An overview of recent research on experimental treatments. Indian J Psychiatry. 2009;51(1):12–25.

257. Bherer L. Cognitive plasticity in older adults: effects of cognitive training and physical exercise. Ann N Y Acad Sci. 2015 Mar;1337:1–6.

258. Ströhle A, Schmidt DK, Schultz F, Fricke N, Staden T, Hellweg R, et al. Drug and Exercise Treatment of Alzheimer Disease and Mild Cognitive Impairment: A Systematic Review and Meta-Analysis of Effects on Cognition in Randomized Controlled Trials. Am J Geriatr Psychiatry Off J Am Assoc Geriatr Psychiatry. 2015 Dec;23(12):1234–49.

259. Wilson RS, Mendes De Leon CF, Barnes LL, Schneider JA, Bienias JL, Evans DA, et al. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. JAMA. 2002 Feb 13;287(6):742–8.

260. Verghese J, Lipton RB, Katz MJ, Hall CB, Derby CA, Kuslansky G, et al. Leisure activities and the risk of dementia in the elderly. N Engl J Med. 2003 Jun 19;348(25):2508–16.

261. Li B, Zhu X, Hou J, Chen T, Wang P, Li J. Combined Cognitive Training vs. Memory Strategy Training in Healthy Older Adults. Front Psychol. 2016 Jun 7;7.

262. Ball K, Berch DB, Helmers KF, Jobe JB, Leveck MD, Marsiske M, et al. Effects of cognitive training interventions with older adults: a randomized controlled trial. JAMA. 2002 Nov 13;288(18):2271–81.

263. Gates NJ, Sachdev PS, Fiatarone Singh MA, Valenzuela M. Cognitive and memory training in adults at risk of dementia: a systematic review. BMC Geriatr. 2011 Sep 25;11:55.

264. Jones RN, Marsiske M, Ball K, Rebok G, Willis SL, Morris JN, et al. The ACTIVE Cognitive Training Interventions and Trajectories of Performance among Older Adults. J Aging Health. 2013 Dec;25(0)

265. Kelly ME, Loughrey D, Lawlor BA, Robertson IH, Walsh C, Brennan S. The impact of cognitive training and mental stimulation on cognitive and everyday functioning of healthy older adults: a systematic review and meta-analysis. Ageing Res Rev. 2014 May;15:28–43.

266. Galante E, Venturini G, Fiaccadori C. Computer-based cognitive intervention for dementia: preliminary results of a randomized clinical trial. G Ital Med Lav Ergon. 2007 Sep;29(3 Suppl B):B26-32.

267. Talassi E, Guerreschi M, Feriani M, Fedi V, Bianchetti A, Trabucchi M. Effectiveness of a cognitive rehabilitation program in mild dementia (MD) and mild cognitive impairment (MCI): a case control study. Arch Gerontol Geriatr. 2007;44 Suppl 1:391–9.

268. Hampstead BM, Sathian K, Moore AB, Nalisnick C, Stringer AY. Explicit memory training leads to improved memory for face-name pairs in patients with mild cognitive impairment: results of a pilot investigation. J Int Neuropsychol Soc JINS. 2008 Sep;14(5):883–9.

269. Belleville S, Bherer L. Biomarkers of Cognitive Training Effects in Aging. Curr Transl Geriatr Exp Gerontol Rep. 2012 Jun;1(2):104–10.

270. Smith GE, Housen P, Yaffe K, Ruff R, Kennison RF, Mahncke HW, et al. A cognitive training program based on principles of brain plasticity: results from the Improvement in Memory with Plasticity-based Adaptive Cognitive Training (IMPACT) study. J Am Geriatr Soc. 2009 Apr;57(4):594–603.

271. Valenzuela M, Sachdev P. Can cognitive exercise prevent the onset of dementia? Systematic review of randomized clinical trials with longitudinal follow-up. Am J Geriatr Psychiatry Off J Am Assoc Geriatr Psychiatry. 2009 Mar;17(3):179–87.

272. Berry AS, Zanto TP, Clapp WC, Hardy JL, Delahunt PB, Mahncke HW, et al. The Influence of Perceptual Training on Working Memory in Older Adults. PLoS ONE. 2010 Jul 14;5(7).

273. Squires EJ, Hunkin NM, Parkin AJ. Errorless learning of novel associations in amnesia. Neuropsychologia. 1997 Aug;35(8):1103–11.

274. Metzler-Baddeley C, Snowden JS. Brief report: errorless versus errorful learning as a memory rehabilitation approach in Alzheimer's Disease. J Clin Exp Neuropsychol. 2005 Nov;27(8):1070–9.

275. Simons DJ, Boot WR, Charness N, Gathercole SE, Chabris CF, Hambrick DZ, et al. Do "Brain-Training" Programs Work? Psychol Sci Public Interest J Am Psychol Soc. 2016 Oct;17(3):103–86.

276. Theill N, Schumacher V, Adelsberger R, Martin M, Jäncke L. Effects of simultaneously performed cognitive and physical training in older adults. BMC Neurosci. 2013 Sep 23;14:103.

277. Eggenberger P, Schumacher V, Angst M, Theill N, de Bruin ED. Does multicomponent physical exercise with simultaneous cognitive training boost cognitive performance in older adults? A 6-month randomized controlled trial with a 1-year follow-up. Clin Interv Aging. 2015 Aug 17;10:1335–49.

278. Lauenroth A, Ioannidis AE, Teichmann B. Influence of combined physical and cognitive training on cognition: a systematic review. BMC Geriatr. 2016 Jul 18;16

279. Chapman SB, Aslan S, Spence JS, Keebler MW, DeFina LF, Didehbani N, et al. Distinct Brain and Behavioral Benefits from Cognitive vs. Physical Training: A Randomized Trial in Aging Adults. Front Hum Neurosci. 2016 Jul 18;10

280. Passow S, Thurm F, Li S-C. Activating Developmental Reserve Capacity Via Cognitive Training or Non-invasive Brain Stimulation: Potentials for Promoting Fronto-Parietal and Hippocampal-Striatal Network Functions in Old Age. Front Aging Neurosci. 2017 Feb 23;9.

281. Küster OC, Fissler P, Laptinskaya D, Thurm F, Scharpf A, Woll A, et al. Cognitive change is more positively associated with an active lifestyle than with training interventions in older adults at risk of dementia: a controlled interventional clinical trial. BMC Psychiatry. 2016 Sep 8;16(1).

282. Dayan E, Censor N, Buch ER, Sandrini M, Cohen LG. Noninvasive brain stimulation: from physiology to network dynamics and back. Nat Neurosci. 2013 Jul;16(7):838–44.

283. Heise K-F, Niehoff M, Feldheim J-F, Liuzzi G, Gerloff C, Hummel FC. Differential behavioral and physiological effects of anodal transcranial direct current stimulation in healthy adults of younger and older age. Front Aging Neurosci. 2014;6:146.

284. Cotelli M, Calabria M, Manenti R, Rosini S, Maioli C, Zanetti O, et al. Brain stimulation improves associative memory in an individual with amnestic mild cognitive impairment. Neurocase. 2012 Jun;18(3):217–23.

285. Meinzer M, Lindenberg R, Phan MT, Ulm L, Volk C, Flöel A. Transcranial direct current stimulation in mild cognitive impairment: Behavioral effects and neural mechanisms. Alzheimers Dement J Alzheimers Assoc. 2015 Sep;11(9):1032–40.

286. Birba A, Ibáñez A, Sedeño L, Ferrari J, García AM, Zimerman M. Non-Invasive Brain Stimulation: A New Strategy in Mild Cognitive Impairment? Front Aging Neurosci. 2017 Feb 13;9.

287. Hsu W-Y, Ku Y, Zanto TP, Gazzaley A. Effects of noninvasive brain stimulation on cognitive function in healthy aging and Alzheimer's disease: a systematic review and meta-analysis. Neurobiol Aging. 2015 Aug;36(8):2348–59.

288. Smith GS, Laxton AW, Tang-Wai DF, McAndrews MP, Diaconescu AO, Workman CI, et al. Increased cerebral metabolism after 1 year of deep brain stimulation in Alzheimer disease. Arch Neurol. 2012 Sep;69(9):1141–8.

289. Sankar T, Lipsman N, Lozano AM. Deep Brain Stimulation for Disorders of Memory and Cognition. Neurotherapeutics. 2014 Jul;11(3):527–34.